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Mensaje del Presidente de la Asociación Médica de Puerto Rico

Raul G. Castellanos Bran, MD MPH FAAFP
Presidente

Reconociendo el impacto sobre la salud y sus repercusiones económicas, en este número se presentan importantes trabajos relacionados con las enfermedades renales en Puerto Rico.

Como introducción al tema y para ubicarlo como un problema de salud pública, “ENFERMEDAD RENAL PERMANENTE EN PUERTO RICO: INCIDENCIA, PREVALENCIA Y MORTALIDAD DE 2000-2008”, presenta amplia información que permite reconocer que a pesar de que existen estrategias para su prevención, el número de casos continúa en aumento. Los datos descriptivos disponibles en el estudio para Puerto Rico, en especial las tasas de incidencia y prevalencia, se compararon con respecto a los Estaos Unidos y otros países. El crecimiento anual promedio en la incidencia y prevalencia fue de 2.4% y 3.0% respectivamente, llevando a la conclusión que la ERP es cada vez más común y prevalente en Puerto Rico.

En la sección Artículos Históricos se nos presenta cómo la invención del Dr. Willem Kolff revolucionó para los años sesenta el tratamiento de los pacientes con enfermedd renal terminal y la aparición de la nefrología como subespecialidad. Para el año 2008 el Departamento de Salud estableció Política Pública y luego se prepararon las Guías Clínicas para el manejo y control del paciente con ERC, por lo que habrá que reevaluarla y hacer los ajustes necesarios.

La Hemoglobinuria Proxística Nocturna es un desorden hematológico raro y causa poco común de hemólisis intravascular, trombosis y supresión de la médula ósea; a partir de una paciente diagnosticada PNH que respondió adecuadamente se discute la patofisiología, manifestaciones clínicas y el tratamiento de esta rara entidad.

La “COMPRESIÓN TRONCO-ENCEFÁLICA POR NEURALGIA DEL TRIGÉMINO EN UN PACIENTE CON DOLICOECTASIA VERTEBRO-BASILAR Y CAROTIDEA BILATERAL”, para los autores, según su conocimiento, es el primer caso de Síndrome Compresivo Troncoencefálico precedido por Neuralgia del Trigémino en paciente con Dolicoectasia Vertebrobasilar y uno de los pocos casos de Dolicoectasia Vertebrobasilar y Carotidea Bilateral.

Se describe el “PRIMARY ANGIOSARCOMA OF THE BREAST IN A PRE-MENOPAUSAL WOMEN”, con esta presentación se completa una tríada de trabajos de entidades poco frecuentes, pero, como en esta, el reconocerla permitirá eventualmetne hacer un diagnóstico temprano y combatirla, para mejorar la sobrevida de los pacientes que la sufren.

Para completar el presente volumen, que incluye importantes estudios de entidades de alta frecuencia a muy poca, está el “HOPEFUL WAITING: POSITIVE OUTCOME OF BLOOD PRESSURE MONITORING IN A EMERGENCY DEPARTMENT”, que concluye que “el monitoreo de la presión arterial cada 30 minutos mejoró significativamente el desenlace clínico de los pacientes que esperaban en la SE y acortó el tiempo total de estadía intrahospitalaria. Contrario las observaciones de la saturación de oxígeno, temperatura corporal y las frecuencias respiratoria y cardíaca no arrojaron resultados significativamente útiles”.

ENFERMEDAD RENAL PERMANENTE EN PUERTO RICO: INCIDENCIA, PREVALENCIA Y MORTALIDAD DE 2000 - 2008

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RESUMEN

Trasfondo: La enfermedad renal permanente (ERP) es un problema mundial de salud pública. A pesar de existir estrategias para su prevención, el número de casos ha ido en aumento. Para conocer la situación actual en Puerto Rico se revisaron datos disponibles que se presentan en este estudio descriptivo sobre las tendencias en la incidencia, prevalencia y mortalidad de ERP durante el periodo 2000 – 2008. Además, se comparan las tasas de incidencia y prevalencia con respecto a otros países del mundo. Métodos: Se utilizaron datos del 'United States Renal Data System' y 'Quality Insights Renal Network' del 2000-2008. Se seleccionaron pacientes en diálisis. Se excluyeron pacientes con trasplante renal. Las tasas de incidencia y prevalencia de PR fueron calculadas. Los datos fueron comparados con tasas de EEUU y otros países del mundo. Resultados: De 2000-2008 la tasa de incidencia aumentó 21.6%, de 286.8 a 348.7 ppm. La tasa de prevalencia aumentó 27.3%, de 861.2 a 1096.2 ppm. El crecimiento anual promedio en la incidencia y prevalencia fue 2.4% y 3.0%, respectivamente. Durante el mismo periodo, la diabetes mellitus fue la principal causa de ERP alcanzando un 67.4% del total de casos nuevos en el 2008, mientras que en EEUU fue 44.4%. La mortalidad disminuyó ligeramente, 18.5% en 2008. PR es el 5to país con mayor incidencia de diálisis y el 1ero en ESRD debido a diagnósticos primarios de diabetes mellitus. Conclusiones: La ERP es cada vez más común y prevalente en Puerto Rico. Se debe ser más agresivo en establecer estrategias de salud pública para reducir la ERP.

Palabras índices: *enfermedad, renal, Puerto Rico, incidencia, prevalencia, mortalidad*

INTRODUCCIÓN

La enfermedad renal crónica (ERC) es reconocida a nivel mundial como un problema importante de salud pública (1-2). La ERC se caracteriza por contar con un alto número de personas afectadas, por tener una distribución desigual en la población y porque existen estrategias de prevención que desafortunadamente no han podido ser puestas efectivamente en práctica (2). De rápida progresión y a la misma vez silente, la ERC impone una carga social, emocional y económica en individuos, familias, sociedad y sistemas de salud (3-6). Los pacientes con ERC tienen una mayor probabilidad de morir a causa de comorbilidades asociadas a la enfermedad renal versus progresar a enfermedad renal permanente (ERP) (7-8).

El número de personas que necesitan y reciben atención para la ERP es desproporcionado en el mundo (9). Por ejemplo, en Taiwán, México y Estados Unidos se reportaron tasas altas de ERP (10). La forma en que las minorías raciales y étnicas, como los afroamericanos e hispanos en Estados Unidos son afectadas es desigual. Por ejemplo, la incidencia de ERP en hispanos es mayor que en blancos no hispanos y los hispanos con ERC tienen un riesgo mayor de progresión a ERP. Posiblemente los factores contribuyentes a esta carga de enfermedad son la diabetes mellitus y el síndrome metabólico, ambas muy comunes en hispanos (2,11).

Un estudio realizado previamente en Puerto Rico indicó que más de 7,000 personas, en su mayoría hombres (61%) iniciaron diálisis principalmente por diabetes mellitus (41.7%) durante el periodo de 1970 - 1994, siendo la modalidad de tratamiento más utilizada la hemodiálisis (76%) (12). Para conocer la situación actual en Puerto Rico se presenta este estudio descriptivo sobre las tendencias en la incidencia, prevalencia y mortalidad de ERP durante el periodo 2000 – 2008. En adición, se comparan las tasas de incidencia y prevalencia con respecto a otros países del mundo.

MATERIALES Y MÉTODOS

Datos agregados de United States Renal Data System (USRDS) y Quality Insights Renal Network 3 (QIRN3) fueron utilizados. USRDS recopila, analiza, y distribuye datos demográficos e información relacionada a la ERP basados en reclamaciones al Centro de Servicios de Medicaid y Medicare (CMS). Se requiere que los proveedores de servicios de salud completen el Informe de Evidencia Médica de los CMS para cada paciente nuevo con ERP. Los datos sólo son disponibles para los pacientes bajo terapias de reemplazo renal que se reportan a los CMS, y no se incluyen aquellos pacientes que mueren antes de recibir tratamiento o cuyo tratamiento no se registra en los CMS. Para extraer los datos de pacientes nuevos y activos (prevalentes) se utilizó la aplicación Renal Data Extraction and Referencing (RenDER), que está accesible a través del portal de USRDS. Para los datos de mortalidad se utilizaron datos provistos por QIRN3, organización contratada por CMS para monitorear la calidad de los servicios a pacientes en diálisis. QIRN3 es una de las 11 fuentes proveedoras de información de USRDS. Estimados de la población de Puerto Rico fueron obtenidos del Negociado del Censo de Estados Unidos (10,13-14).

Un caso de ERP se define como aquella persona registrada para recibir terapia de reemplazo renal, ya sea diálisis o trasplante. Los casos nuevos o incidencia se definen como el número de personas con nuevos diagnósticos en la población durante un periodo dado, comúnmente un año. La prevalencia es el número de personas en la población que tienen la enfermedad en un punto definido en el tiempo o durante un periodo.

En la selección de variables de estudio sólo se incluyeron datos de Puerto Rico y las modalidades de hemodiálisis y diálisis peritoneal, y fue excluida la modalidad de trasplante renal. Las variables seleccionadas fueron grupos de edades en decenios, sexo y diagnóstico primario de diabetes mellitus, hipertensión, glomerulonefritis, enfermedad renal poliquística y otros.

Se calcularon los porcentajes, tasa de cambio porcentual, tasa promedio de crecimiento anual y las tasas crudas de morbilidad y mortalidad. Se realizó una comparación de las variables demográficas y diagnóstico primario entre Puerto Rico y EEUU para el 2008. Por último, se compararon las tasas de morbilidad de Puerto Rico con respecto a las tasas de incidencia y prevalencia de regiones y países del mundo. Para realizar los cálculos se utilizó Excel 2010.

RESULTADOS

Durante el periodo 2000 – 2008 hubo un total de 11,330 casos nuevos. Este número aumentó 26.1%, de 1,094 casos en el 2000 a 1,379 casos en el 2008. El crecimiento promedio anual en el periodo fue 2.6%. Mientras, la tasa de incidencia aumentó 21.6%, de 286.8 en el 2000 a 348.7 casos por millón de habitantes en el 2008. Esto representó un crecimiento anual promedio en la tasa de incidencia de 2.2% (ver Tabla 1).

Para el año 2008, la razón hombre: mujer fue 2:1, lo que significa que por cada mujer hay dos hombres recibiendo diálisis. La distribución por grupos de edades (decenios) para el año 2008, muestra que la mayor proporción de casos nuevos ocurren en la sexta (29.8%), séptima (22.8%) y quinta (20.4%) década de vida. La mayoría de las personas que inician diálisis (73.0%) están entre 50 y 79 años. La principal causa de ERP en Puerto Rico es la diabetes mellitus (67.4%) seguido de la hipertensión (12.8%). Ambas enfermedades contribuyen en un 80% a la ERP. Otros diagnósticos relacionados son las nefritis y la enfermedad renal poliquística (ver Tabla 2).

De manera similar, el número de casos prevalentes aumentó 32.0%, de 3,285 casos en el 2000 a 4,335 casos en el 2008. La tasa promedio de crecimiento anual durante el periodo fue 3.1%. La tasa de prevalencia aumentó 27.3%, de 861.2 casos en el 2000 a 1096.2 casos por millón de habitantes en el 2008, con una tasa promedio de crecimiento anual para el periodo de 2.7% (ver Tabla 1).

Las características de sexo, grupos de edades y diagnósticos primarios en pacientes que reciben diálisis muestran patrones similares a los observados en el indicador de incidencia (ver Tabla 2).

Un total de 8,912 pacientes de diálisis fallecieron durante el periodo 2000 – 2008. Este número aumentó 13.3%, de 904 casos en 2000 a 1,024 casos en 2008, lo que representa un aumento promedio anual de 1.4%. De forma similar, el número de casos a riesgo de morir, que son representados por los nuevos y prevalentes durante el año aumentó un 28.2%, de 4,317 en 2000 a 5,533 casos en 2008.

Aunque el número de muertes aumentó durante el periodo, se encontró una ligera disminución de un 1.5% en la tasa cruda de mortalidad, de 20.9% en 2000 a 18.5% en 2008. Causas como las enfermedades cardiacas (33.6%), vasculares (8.3%) y las infecciones (30.0%) son las de mayor ocurrencia y las responsables de la mayoría de las muertes en pacientes en diálisis. La Tabla 3 describe la distribución de las características de sexo, grupos de edades y diagnóstico primario para diálisis en los pacientes que murieron durante el 2008.

Tabla 1. Número y Tasa de Incidencia, Prevalencia y Mortalidad de Enfermedad Renal Permanente – Puerto Rico, 2000-2008

Año	INCIDENCIA		PREVALENCIA		MORTALIDAD	
	Núm.	Tasa*	Núm.	Tasa*	Núm	Tasa*
2000	1,094	286.8	3,285	861.2	904	20.9
2001	1,163	303.0	3,335	869.0	975	21.9
2002	1,212	314.1	3,447	893.4	991	21.8
2003	1,281	330.4	3,529	910.3	1,066	22.5
2004	1,293	332.1	3,658	939.4	1,017	21.1
2005	1,230	314.5	3,751	959.2	955	19.5
2006	1,321	336.4	3,986	1,015.1	959	18.9
2007	1,357	344.3	4,154	1,054.0	1,021	19.1
2008	1,379	348.7	4,335	1,096.2	1,024	18.5
Periodo 2000-2008						
Total	11,330	-	-	-	8,912	-
Δ%	26.1	21.6	32.0	27.3	13.3	-11.6
Tasa Crec. Anual (%)	2.6	2.2	3.1	2.7	1.4	-1.4

Fuente: PR Renal Health and Research; *Tasas de Incidencia y Prevalencia (no ajustadas) por millón de habitantes de PR. Tasa cruda de mortalidad (%)
Δ% = Cambio Porcentual y Tasa de Crecimiento Anual Promedio (%)
USRDS (RenDER): Número de Casos Nuevos y Prevalentes. Quality Insights Renal Network 3 (QIRN3): Número de muertes.

Tabla 2. Enfermedad renal permanente, por sexo, grupo de edades y diagnóstico primario – Puerto Rico, 2000 y 2008

	INCIDENCIA						PREVALENCIA					
	2000		2008		(2000-2008)		2000		2008		(2000-2008)	
Características	Núm.	%	Núm.	%	Δ %	Tasa Crec. Anual (%)	Núm.	%	Núm.	%	Δ %	Tasa Crec. Anual (%)
Sexo												
Masculino	649	59.3	834	60.5	28.5	2.8	2,027	61.7	2633	60.7	29.9	2.9
Femenino	445	40.7	545	39.5	22.5	2.3	1,258	38.3	1702	39.3	35.3	3.4
Grupo de Edades												
00-09	1	0.1	1	0.1	0	0.0	4	0.1	2	0.0	-50	-7.4
10-19	13	1.2	6	0.4	-53.8	-8.2	19	0.6	14	0.3	-26.3	-3.3
20-29	41	3.7	34	2.5	-17.1	-2.1	107	3.3	112	2.6	4.7	0.5
30-39	57	5.2	60	4.4	5.3	0.6	241	7.3	251	5.8	4.1	0.5
40-49	122	11.2	145	10.5	18.9	1.9	449	13.7	530	12.2	18	1.9
50-59	239	21.8	281	20.4	17.6	1.8	848	25.8	927	21.4	9.3	1.0
60-69	331	30.3	411	29.8	24.2	2.4	939	28.6	1,362	31.4	45	4.2
70-79	205	18.7	315	22.8	53.7	4.9	514	15.6	832	19.2	61.9	5.5
80+	85	7.8	126	9.1	48.2	4.5	164	5	305	7.0	86	7.1
Diagnóstico Primario												
Diabetes Mellitus	689	63	930	67.4	35	3.4	1636	49.8	2568	59.2	57	5.1
Hipertensión	148	13.5	177	12.8	19.6	2.0	554	16.9	662	15.3	19.5	2.0
Nefritis	105	9.6	93	6.7	-11.4	-1.3	607	18.5	514	11.9	-15.3	-1.8
PKD	15	1.4	28	2	86.7	7.2	102	3.1	119	2.7	16.7	1.7
Otros	137	12.5	151	10.9	10.2	1.1	386	11.8	119	10.9	22.3	2.3

Fuente: PR Renal Health and Research - Porcentajes, Δ% = Cambio Porcentual y Tasa de Crecimiento Anual Promedio. USRDS: Número de Casos Nuevos y Prevalentes.
PKD = Enfermedad Renal Poliquística (Polycystic Kidney Disease, PKD, por sus siglas en inglés) Nefritis (Todas las glomérulonefritis).

Comparación con Estados Unidos

En Estados Unidos (EEUU) la incidencia y prevalencia han ido en constante aumento. Por ejemplo, durante el periodo 2000 – 2008 hubo un total de 906,119 casos nuevos. Este número aumentó 18.0%, de 91,311 casos en 2000 a 107,711 casos nuevos de diálisis en 2008. El crecimiento promedio anual en el periodo fue 1.9%, menor (0.7%) al crecimiento observado durante el mismo periodo para Puerto Rico.

En EEUU a tasa de incidencia aumentó 9.4%, de 323.6 casos en el 2000 a 353.9 casos por millón de habitantes en el 2008, con un crecimiento anual promedio de 1.0%. Las diferencias en las proporciones entre Puerto Rico y EEUU son notables, experimentando la Isla un crecimiento mayor durante el periodo (26.1% vs. 18.0%).

Con respecto a los casos prevalentes en EEUU, el número aumentó 34.8%, de 278,620 casos en 2000 a 375,687 casos en 2008.

Tabla 3. Mortalidad de la Enfermedad Renal Permanente, por sexo, grupo de edades y características seleccionadas – Puerto Rico, 2008

Características		Mortalidad	
		Núm	%
Sexo	Masculino	617	60.3
	Femenino	407	39.7
Grupo de Edades	00-09	1	0.1
	10-19	0	0.0
	20-29	10	1.0
	30-39	37	3.6
	40-49	81	7.9
	50-59	161	15.7
	60-69	302	29.5
	70-79	279	27.2
	80+	153	14.9
Diagnóstico Primario	Diabetes Mellitus	680	66.4
	Hipertensión	138	13.5
	Glomérulonefritis	61	6.0
	Enfermedad Renal Poliquística	28	2.7
	Otros	117	11.4
Causas de Muerte	Cardiacas	344	33.6
	Vasculares	83	8.3
	Infecciones	299	30.0

.El número de casos aumentó en promedio anualmente a razón de 3.4%. Mientras, la tasa de prevalencia aumentó 25.0%, de 987.4 casos en 2000 a 1234.3 casos por millón de habitantes en 2008. La tasa promedio de crecimiento anual para la prevalencia durante el periodo fue 2.5%, 0.2% menor a la de Puerto Rico.

En EEUU las principales causas de ERP para el año 2008 fueron la diabetes mellitus e hipertensión (44.4% y 28.6%). Durante el periodo 2000 – 2008 el número de casos nuevos en diálisis con diagnóstico primario de diabetes mellitus aumentó 15.9%, de 41,294 casos en el 2000 a 47,854 casos en el 2008. Mientras, el número de casos prevalentes con diagnóstico primario de diabetes mellitus aumentó 45.1%, de 113,023 en el 2000 a 163,951 casos en el 2008. El promedio de crecimiento por año de los casos nuevos con diagnóstico primario de diabetes mellitus fue 1.7% mientras que en los casos prevalentes fue 4.2%.

La proporción de casos nuevos con diagnóstico primario de diabetes mellitus es mucho mayor en Puerto Rico que en EEUU (67.4% vs. 44.4%). La proporción de casos que aumentó durante el periodo fue más del doble que la de EEUU (35.0% vs. 15.9%) evidenciado por un promedio de crecimiento anual más bajo en EEUU que en Puerto Rico (1.7% vs. 3.4%). Sobre los casos prevalentes con diagnósticos primarios de diabetes mellitus tanto Puerto Rico como EEUU presentan un aumento grande en la proporción de casos (5.1% vs. 4.2%) y un incremento en la tasa de crecimiento anual promedio (5.1% vs. 4.2%).

Tabla 4. Comparación de las Tasas de Incidencia, % de Casos Nuevos de ERP por Diagnóstico Primario de Diabetes Mellitus y Tasas de Prevalencia de las Regiones/ Países y Puerto Rico,

Región o País	Tasa de Incidencia	Región o país	% de Casos Nuevos Por Diagnóstico Primario de Diabetes Mellitus	Región o País	Tasa de Prevalencia
1. Morelos, México	557	**1. PUERTO RICO**	**67.4**	1. Taiwán	2288
2. Jalisco, México	400	2. Morelos, México	59.8	2. Japón	2060
3. Taiwán	384	3. Malasia	55.8	3. Estados Unidos	1698
4. Estados Unidos	362	4. Jalisco, México	54.6	4. Alemania	1114
5. PUERTO RICO	**348.7**	5. Nueva Zelandia	45.5	5. Bélgica (Francesa)	1109
6. Japón	288	6. Taiwán	44.4	**6.PUERTO RICO**	**1096.2**
7. Turquía	261	7. EEUU	43.8	7. Bélgica (Alemana)	1073
8. Luxemburgo	227	8. Japón	43.2	8 Israel	1041
9. Grecia	199	9. República de Corea	41.9	9. Canadá	1037
10. Bélgica	190	10. Israel	41.4	10. Hong Kong	1027

Resumen: PR Renal Health and Research, Inc. Tasas de Incidencia y Prevalencia son no ajustadas.
Datos de regiones/países: U S Renal Data System, USRDS 2010 Annual Data Report.

Para el 2008, la mayoría (66.0%) de los pacientes recibiendo tratamiento para la ERP en EEUU se encuentran entre los 50 y 79 años de edad, proporciones similares a las presentadas para Puerto Rico. Mientras que la distribución por sexo (hombre: mujer) fue similar en EEUU y Puerto Rico, aunque existe un porcentaje mayor de mujeres recibiendo tratamiento para la ERP en EEUU comparado con Puerto Rico (45.9% vs. 39.3%).

Comparaciones Internacionales

Las tasas de incidencia de ERP por millón de habitantes fueron mayores en la regiones de Morelos y Jalisco, México, en Taiwán y en EEUU con 557, 400, 384 y 362 casos por millón de habitantes, respectivamente. Puerto Rico tiene una tasa de incidencia de 348.7 casos por millón de habitantes, ubicándose en la 5ta posición con respecto a las demás regiones y países del mundo. Le siguen Japón, Turquía, Luxemburgo, Grecia, Bélgica e Israel con 288, 261, 227, 199, 198 y 189 casos por millón de habitantes.

Países como Taiwán, EEUU, Japón, Luxemburgo, Grecia, Bélgica e Israel son desarrollados y tienen ingresos per cápita que sobrepasan los $30,000 ($29,500 - $81,000). Turquía, México y Puerto Rico reportan un ingreso per cápita mucho menor, desde $12,300 – $16,300 (15). Los países desarrollados tiene como característica un mayor envejecimiento poblacional, con proporciones que van entre 9.9% en Israel hasta 22.2% en Japón. Con respecto a los factores demográficos, Puerto Rico cuenta con una alto porcentaje (14.1%) de personas ≥ 65 años (15). Esta proporción es comparable con el resto de países desarrollados y que tienen cifras altas de pacientes en tratamiento de la ERP.

Anteriormente se presentó la elevada proporción de casos de diagnóstico primario de diabetes mellitus iniciando tratamiento para ERP, lo que al comparar con el resto de países posiciona a PR en el primer lugar en este renglón. Esta es mayor que México y Malasia, cuyas proporciones son 59.8% y 55.8%, respectivamente. Los países con prevalencias más altas son Taiwán, Japón, Estados Unidos, Bélgica, Canadá, Israel, Hong Kong, Chile y Francia. Puerto Rico se ubica en la sexta posición, al igual que Canadá, con 1,096 casos por millón de habitantes para el año 2008. Otras naciones no industrializadas o en desarrollo, no se encuentran en este resumen porque probablemente no cuentan con registros adecuados de enfermedades crónicas.

DISCUSIÓN

Este estudio descriptivo presenta un resumen actualizado de las tendencias de la incidencia, prevalencia y mortalidad de ERP durante el periodo 2000 – 2008, y una comparación de las situación en Puerto Rico, EEUU y otros países del mundo.

La ERC sigue siendo un problema importante de salud pública (1-2) que va en crecimiento, con una alta carga económica, morbilidad y mortalidad para la sociedad a pesar de la disponibilidad de guías terapéuticas y evidencias médicas de retardo de la evolución de ERP con intervenciones terapéuticas realizadas en forma precoz en etapas tempranas para demorar o evitar la diálisis.

Un patrón de incremento continuo durante nueve años estudiados fue observado en las tasas de incidencia y prevalencia (no ajustadas) de ERP en Puerto Rico. El crecimiento en el número de casos nuevos y tasa de incidencia (26.1% y 21.6%, respectivamente) pudiera sugerir una mayor presencia de factores relacionados con la ERC, como la diabetes mellitus e hipertensión que conducen a ERP. Otros factores como el aumento en el envejecimiento poblacional y cambios en los patrones de diagnósticos de la enfermedad pudieran contribuir a que un número mayor de personas estén siendo diagnosticadas más efectivamente. La prevalencia mostró un patrón similar de crecimiento lo que sugiere una relación con la disminución en la mortalidad, el aumento en la incidencia y el acceso a servicios médicos.

Aunque la mortalidad ha mostrado una ligera disminución durante el periodo, la misma se considera aún muy elevada. La mortalidad en la ERP sobrepasa la cifra de los mil casos, y además ocurre mayormente en pacientes que han sido referidos tardíamente, que exhiben condiciones crónicas pobremente manejadas y que hacen mayor utilización de accesos vasculares como los catéteres.

Para el 2008, al igual que el resto del periodo, la proporción hombre mujer (2:1) se mantuvo constante. Se desprende de dicha relación observada que la ERP es una enfermedad de mayor ocurrencia en hombres y que probablemente el género femenino pudiera ser afectado por diversos factores en etapas tempranas de la ERC, como por ejemplo enfermedades comórbidas como las cardiovasculares, cerebrales, diabetes mellitus y obesidad. En EEUU, la diferencia por género es más reducida (hombres: 54.1% vs. mujeres: 45.9%) lo cual contribuye a la sugerencia de que se realicen estudios evaluando factores que pudieran estar asociados a estas diferencias.

La alta proporción observada en los grupos de edades mayores a los 50 años sugiere que en la mayoría de los casos se necesita de un periodo largo para que ocurra la ERP como consecuencia de enfermedades que la anteceden. A nivel general, se estima que hay más de 500,000 personas (12.9%) diagnosticados con diabetes mellitus en PR y que basado en esos datos, pudiera existir una proporción mayor de personas que desconocen que tienen esta enfermedad (16). El 30% de los casos nuevos de ERP ocurrió en pacientes en la 6ta década de la vida, seguida de la 7ma y la 5ta década, lo cual coincide con la modificación en la pirámide de la población puertorriqueña que es una cada vez más vieja. Más aún, se destaca el subgrupo de 80 años o más el cual presentó una alta proporción en aumento. Esto pudiera deberse a un mejor acceso a los servicios, a un mejorado sistema de salud en comparación a años anteriores o quizás a una mayor sobrevivencia de personas con la enfermedad (10).

En EEUU la incidencia y prevalencia (no ajustada) es mayor que en PR. Sin embargo, la proporción de casos nuevos con diagnóstico primario de diabetes es mucho mayor en PR que en EEUU. A diferencia de las tendencias en la Isla, en EEUU la incidencia de ERP ha mostrado un patrón de reducción. Según USRDS, la tendencia de la tasa de incidencia ajustada en EEUU ha disminuido desde el año 2001. Con relación a las tasas de incidencia de ERP por diabetes en EEUU, estas han aumentado en jóvenes de grupos minoritarios, han sido estables o se han reducido en las poblaciones de mayores de 65 años y blancas, por lo tanto se requiere una evaluación más detallada de estas subpoblaciones para determinar si las tendencias son coincidentes entre todos los subgrupos (10). De acuerdo a los datos disponibles Puerto Rico es el 5to país con mayor incidencia – el 1ero en diagnostico primario de diabetes – y 6to en mayor prevalencia por millón de habitantes. Solamente es superado por regiones de México (Jalisco y Morelos), Taiwán y EEUU (10). Los sistemas de salud de cada una de estas regiones o países son únicos y sus características demográficas y económicas también. En relación a la incidencia y prevalencia, de los países comparados con Puerto Rico, la mayoría tienen altos ingresos per cápita y sistemas avanzados de provisión de servicios de salud y cuidados públicos para manejar las principales enfermedades crónicas. Por ejemplo, Taiwán y Japón reciben cubiertas de cuidado universal y las terapias de diálisis han estado disponibles por muchos años por lo tanto en estas características ambos se parecen a PR. Para el tratamiento a los pacientes nuevos con ERP se puede distinguir la disponibilidad de fondos para guiar el cernimiento y tratamiento de los pacientes. A diferencia de países desarrollados, en países pocos desarrollados miles de pacientes mueren anualmente por no tener facilidades disponibles para cubrir las necesidades de la población renal (17). Las naciones afluentes pueden permitir a personas con edad mayor de 65 años y a personas con diabetes mellitus a recibir hemodiálisis, mientras que las naciones en vías de desarrollo pueden restringir el tratamiento a personas más jóvenes y saludables (10). En estos países, al igual que en Puerto Rico, el diagnóstico primario debido a glomérulonefritis continúa en descenso y se sugiere que esta disminución puede deberse a que los casos se diagnostican bajo inferencias clínicas a diferencia de realizarse diagnósticos patológicos definitivos.

Este estudio se basó en datos existentes los cuales pueden estar potencialmente afectados por las definiciones de los numeradores y denominadores, y por el hecho de que las tasas sean no ajustadas. La tendencia actual en Puerto Rico sugiere que hay serias necesidades médicas sin resolver que requieren mayor investigación.

Consciente de las implicaciones éticas, sociales y económicas de la enfermedad renal en Puerto Rico se creó el Modelo de Salud Renal (Modelo de Referencia y Contra-referencia) en el 2005 y en el 2008 se estableció la Política Pública para la Salud Renal de los Adultos en Puerto Rico y la Guía de Prevención y Detección Temprana de la ERC (18-20), para ser utilizado como instrumentos para reducir la incidencia por medio de la prevención de la enfermedad renal. Por todo lo antes discutido, es obvio que se debe ser más agresivo en implantar la política pública ya que no están siendo puestas en marcha adecuadamente.

Todos los esfuerzos se deben orientar a realizar una mejor medición y control de la presión arterial, en la detección de proteinuria, en el cálculo de la filtración glomerular, en el control de la glucosa y del peso, así como la referencia temprana del paciente renal al nefrólogo en la etapa 4 de ERC, para la construcción efectiva de accesos vasculares, entre otros.

La información presentada debe servir para de forma integrada establecer una mejor vigilancia, concienciación, tratamiento y control de los factores de riesgo de enfermedad renal crónica. El cuidado de un paciente renal no pertenece solo al nefrólogo, también es responsabilidad del médico primario, del mismo paciente, del gobierno, en fin de la sociedad en general. La enfermedad renal crónica es común y devastadora. Se debe actuar con premura para establecer un plan de acción efectivo encaminado a la prevención de la enfermedad renal crónica en Puerto Rico.

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ABSTRACT

Background: End-Stage Renal Disease (ESRD) is a global public health problem. Although there are strategies for its prevention, the number of cases has increased. In order to understand current situation in Puerto Rico (PR) we review available data, which is presented in a descriptive report of the incidence, prevalence and mortality of ESRD during the period 2000-2008. In addition, we compare the incidence and prevalence rates with regard to other countries. Methods: We used 2000-2008 USRDS statistics and the QIRN3 for patients on dialysis. Transplanted patients were excluded. Crude rates of incidence and prevalence in PR were calculated for comparison with the United States and other countries. Percentages were calculated to describe the demographic characteristics and primary diagnosis in 2008. Results: During the period 2000-2008 the incidence rate increased by 21.6 percent; from 286.8 to 348.7 pmp. The prevalence rate increased by 27.3 percent; from 861.2 to 1096.2 pmp. The average annual growth in the incidence and prevalence was 2.4 percent and 3.0 percent respectively. During the same period, diabetes mellitus was the leading cause of ESRD reaching 67.4 percent of total new cases in 2008, while in the U.S. was 44.4 percent. Unadjusted mortality decreased slightly in 2008 to 18.5 percent. PR is the fifth country with the highest incidence of patient on dialysis and the first with ESRD due to diabetes mellitus. Conclusions: ESRD is becoming more common and prevalent in PR. We should be more aggressive in establishing public health strategies to reduce ESRD.

REGISTRY OF KIDNEY BIOPSY IN A SINGLE CENTER IN PUERTO RICO: UNIVERSITY DISTRICT HOSPITAL

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ABSTRACT

Glomerular diseases continue to be the leading cause of end-stage renal disease globally. Renal biopsy plays a fundamental role in the evaluation of glomerular diseases not only to establish an accurate diagnosis but also help deciding on appropriate treatment and assessing prognosis. The prevalence of glomerular disease and the clinical indications for kidney biopsies are poorly delineated in Puerto Rico. We undertook a retrospective analysis of the indications, clinical presentation and pathologic reports in renal biopsies performed at the University District Hospital in San Juan, Puerto Rico from the year 1995 to 2008. A total of 208 kidney biopsies showed a predominance of membranous nephropathy representing 20% of the studied population. Women were more frequently biopsied than men (57.2% vs. 42.7%). Lupus nephritis, a condition affecting mostly women was identified in 16.9% of the patients. Minimal change disease was reported in 13.6% of the patients, a condition that affects mostly children and adolescents. In contrast to other geographical areas IgAN was reported only in 6.3% and FSG in 0.9% of patients. In our biopsied patient population, membranous nephropathy is the most common primary glomerular disease and lupus erythematosus the most frequent secondary glomerular disease.

Index words: *registry, kidney, biopsy, University District Hospital*

INTRODUCTION

Glomerular diseases continue to be the leading cause of end-stage renal disease globally. It represents the most common cause of end-stage renal disease in many countries. Its pattern, however, differs according to the geographical area.

Glomerular diseases may be categorized into those that primarily involve the kidney (Primary Glomerular Diseases), and those in which the kidney involvement is part of a systemic disorder (Secondary Glomerular Diseases) 1. The glomeruli are affected by a variety of environmental insults and systemic disorders aside from the primary glomerulopathies. Glomerular diseases generally present with variable degrees of proteinuria, hematuria, hypertension and/or impaired renal function. Some glomerular diseases may be indolent and develop into insidious uremia (2).

Renal biopsy plays a fundamental role in the evaluation of glomerular diseases not only to establish an accurate diagnosis but also to help deciding on appropriate treatment and assessing the prognosis.

IgA nephropathy represents the majority of the primary glomerular diseases and is the most important cause of end-stage renal failure (3). Membranous nephropathy has been traditionally considered the most common cause of nephritic syndrome in adults (1). Some studies, mostly from Europe reported a change in the pattern of glomerular diseases in the community (4).

According to these, focal segmental glomerulosclerosis is increasing in incidence and now accounts for 20 to 25% of all nephritic syndrome cases (5). Furthermore, a study published in 2000 from the United States has shown focal segmental glomerulosclerosis (FSG) to be the most common idiopathic glomerular disease in adults(5). However, the increasing incidence of FSG was seen only in the Black (22.6%) and Hispanic (24.6%) populations and not in white individuals. For this reason, the findings of that study may not be generalized to the entire population of the United States, where 75% of the total population is white.

In the literature there is limited population based epidemiological data on the spectrum of biopsy proved glomerular disease (11). A review of renal biopsy data can give some insight into the spectrum of clinically significant renal disease in our community.

The prevalence of glomerular disease and the clinical indications for kidney biopsies are poorly delineated in Puerto Rico. We undertook a retrospective analysis of the indications, clinical presentation and pathologic reports in renal biopsies performed at the University District Hospital in San Juan, Puerto Rico from the year 1995 to 2008.

SUBJECTS AND METHODS

A retrospective study was performed by reviewing the renal biopsy logbook at the Nephrology section. We reviewed renal biopsies performed during a fourteen year period (February 1995 to November 2008).

A total of 230 kidney biopsy reports were reviewed in our study. Only native kidney biopsies of adults were included. We excluded a total of 22 of which 12 were renal transplant patients and 10 had no definitive diagnosis.

We obtained the clinical presentation, biopsy indications and frequency of glomerular diseases in the time period previously stated. All biopsies were studied and analyzed using light, electron microscopy and immunofluorescence techniques.

Demographic data showed 189 women (57.2%) and 89 men (42.7%). Their median age was 37 + 14.2 years old.

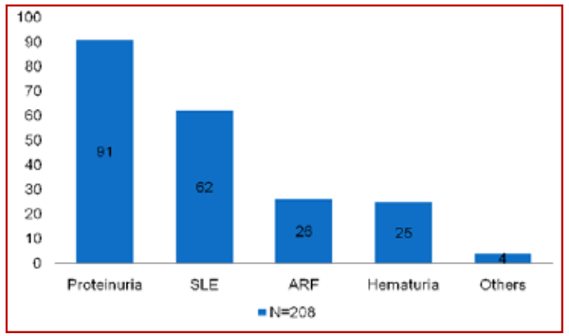


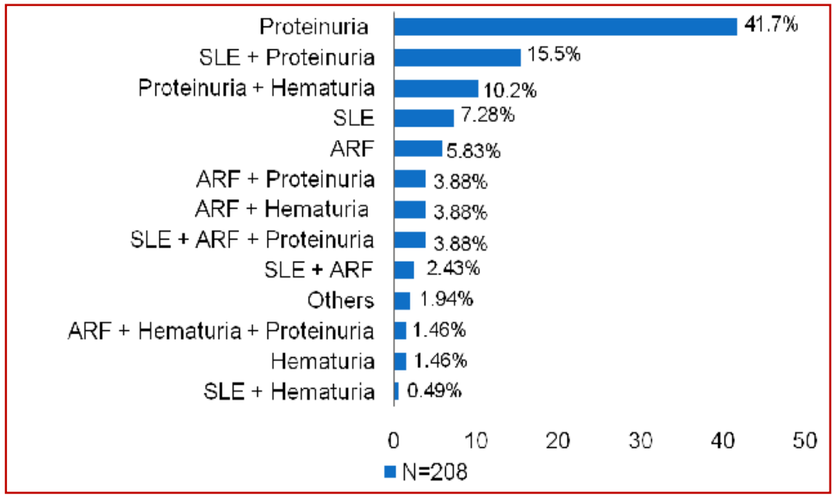
Figure 1 shows the frequency and indications for kidney biopsy. Proteinuria was the indication in 91% of cases, Systemic lupus Erythematosus (SLE) in 62%, acute renal failure in 26%, hematuria in 25% and others in 4% of cases

RESULTS

Figure 1 shows the frequency and indications for kidney biopsy. Proteinuria was the indication in 91% of cases, Systemic lupus Erythematosus (SLE) in 62%, acute renal failure in 26%, hematuria in 25% and others in 4% of cases.

Figure 2 shows the indications according to the clinical presentation. Proteinuria alone was the indicator in 41.7% of cases. SLE and Proteinuria in 15.51%, proteinuria and hematuria in 10.2%, SLE in 7.28%, acute kidney injury(AKI) in 5.83%, acute kidney injury and proteinuria in 3.88%, SLE in 7.28%, AKI and proteinuria in 1.46@, hematuria alone in 1.46% and SLE and hematuria in 0.49% of cases.

Figure 3 shows the frequency of pathologic reports of renal biopsies performed during 1995 to 2008. Membranous glomerulonephritis was the most frequent diagnosis with 29%, SLE 16.9%, Chronic tubulointerstitial nephritis 14.5%, minimal change disease in 13.1%, Mesangial glomerulonephritis (mesangial GMN) in 10.6% Immunoglobin A nephropathy in 6.3%, Chronic GMN in 2.4%, normal pathology in 2.4% and focal segmental sclerosis in 0.9%.



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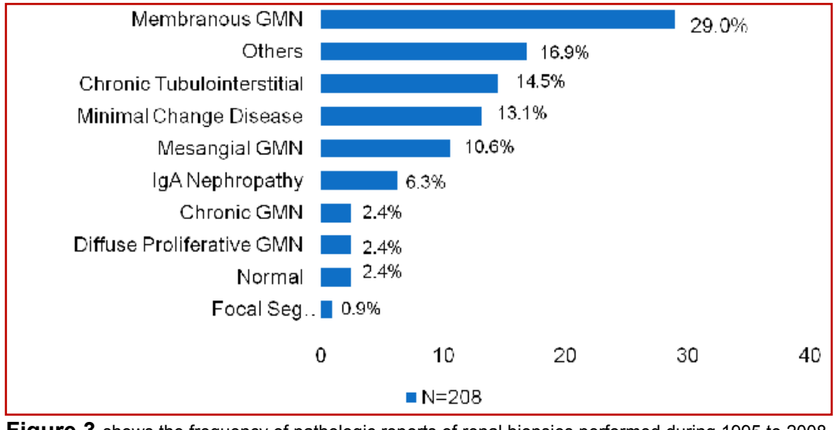

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DISCUSSION

n a single medical center in Puerto Rico, the University District Hospital a 14-year registry of 208 kidney biopsies showed a predominance of membranous nephropathy representing 20% of the studied population. Women were more frequently biopsied than men (57.2% vs 42.7%). Lupus nephritis, a condition affecting mostly women was identified in 16.9% of the patients. Minimal change disease was reported in 13.6% of the patients, a condition which affects mostly children and adolescents. Tubulo-interstitial nephritis was also reported in 14.6% of the studied population. In contrast to other geographical areas IgAN was reported only in 6.3% and FSG in 0.9% of patients.

The University District Hospital is a referral hospital which covers a population over 1 million inhabitants in a metropolitan area. Patients for kidney biopsy are referred to the Nephrology Section and evaluated extensively before kidney biopsy is performed. Patients with documented history of diabetes with or without nephropathy are not usually biopsied. Similarly, patients with microscopic hematuria are not biopsied unless there is renal insufficiency or a strong suspicion of IgAN.

The pattern of primary glomerular disease occurring in this special Hispanic population is unique in its high prevalence of membranous nephropathy. The etiology of primary glomerular disease is unknown and recent studies have advanced possible mechanisms (6).

The most prevalent secondary glomerular disease among this group of patients is SLE (16.9%). In Puerto Rico, SLE is a common condition among our women and affects the kidney in most cases.

The findings are in contrast with other renal biopsy registry reports in other countries. For example in Spain (7), India(8), Japan (9), China(10), Australia(11) and Italy(12). IgAN constitute the most frequent primary diagnosis. On the other hand FSGS is the commonest primary glomerular disease in Medellin, Colombia (13) and in studies which included Afro-American and Hispanic Patients (6).

There are attenuating factors in this type of report. First it is a small population for one single center although the University District Hospital is the referral center to examine kidney biopsies for the island. Second, indications for kidney biopsy were limited and did not include diabetic patients and a greater number of patients with microscopic hematuria alone.

In conclusion, in our biopsied patient population, membranous nephropathy is the most common primary glomerular disease and lupus erythematosus the most frequent secondary glomerular disease. IgAN and FGS were not frequently observed as reported in other geographical regions in the world.

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RESUMEN

Las enfermedades glomerulares son la mayor causa de enfermedad renal a nivel mundial. Su patrón, sin embargo se diferencia de acuerdo a su distribución geográfica. La biopsia de riñón tiene un rol fundamental en la evaluación de las enfermedades glomerulares no solo para establecer un diagnóstico adecuado, sino para asegurar el tratamiento indicado y su pronóstico. La prevalencia de enfermedades glomerulares y las indicaciones para biopsias de riñón no están descritas en Puerto Rico. Se realizó análisis retrospectivo de las indicaciones, presentación clínica y reportes de patología en biopsias de riñón en el Hospital Universitario en San Juan, Puerto Rico desde el año 1995 hasta 2008. En el centro estudiado se obtuvo un total de 208 biopsias de riñón, las cuales mostraron una predominancia de nefropatía membranosa en un 20% de la población estudiada. Las biopsias en mujeres fueron más frecuentes que en hombres (57.2% vs 42.7%). Nefritis por Lupus, una condición que afecta mayormente a mujeres se identificó en un 16.9% de los pacientes. Enfermedad de cambio mínimo, se reportó en un 13.6% de los pacientes, una condición que afecta en la mayoría de los casos a niños y adolescentes. Contrario a otras áreas geográficas, nefropatía por IgA, se encontró en solo 6.3% y glomerulonefritis focal segmentada en un 0.9% de los pacientes. En conclusión en nuestras biopsias la nefropatía membranosa es la enfermedad primaria glomerular mas común y el lupus eritematoso la enfermedad glomerular secundaria mas común.

LIFE THREATENING HYPERKALEMIA IN CHRONIC KIDNEY DISEASE PATIENTS TREATED WITH TRIMETHOPRIM-SULFAMETHOXAZOLE: A Case Series

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ABSTRACT

We report a case series of patients that develop severe life threatening hyperkalemia after use of a commonly prescribe oral antibiotic, Trimethoprim-Sulfamethoxazole. The three patients required acute hemodialysis to normalize serum potassium levels after development of hypotension and heart block due to hyperkalemia. All had preexisting chronic kidney disease. Some of them were on medications that interfere with the effects of aldosterone. Patients with chronic kidney disease, particularly those receiving other medications that may also contribute to the development of hyperkalemia, should be closely monitored for this complication when Trimethoprim-containing antibiotic is needed. In these cases, other antibiotic therapy alternatives should be considered.

Index words: *hyperkalemia, chronic, kidney, disease, trimethoprim, sulfamethoxazole*

INTRODUCTION

Trimethoprim-Sulfamethoxazole (TMP/SMX) is an antibiotic which is commonly utilized for the treatment of uncomplicated urinary tract infections (UTI) and as prophylaxis of infections such as Pneumocystitis Jirovenci in immunosuppresed patients. This medication also has action on the principal cell of the nephron cortical collecting duct where it decreases the kidney's ability to excrete potassium. Due to this effect, patients with chronic kidney disease (CKD) are at risk of developing clinically significant hyperkalemia in part due to the reduction in potassium renal handling capacity, and the concomitant use of medications that alter potassium excretion. These medications include but are not limited to Angiotensin Converting Enzyme inhibitors (ACEI), Angiotensin II receptor blockers (ARBS), and β-blockers. We present a case series of three patients with CKD admitted with severe hyperkalemia at the Veterans Affairs Caribbean Healthcare System Hospital in San Juan.

Case 1

71-years-old man with a history of CKD secondary to diabetes mellitus Type II with baseline serum creatinine level of 1.9 mg/dl. He presented to Emergency Department (ED) with hypoactivity and diffuse muscle pain for the past 24 hours. Five days prior to presentation the patient was prescribed TMP/SMX, two tablets every 12 hours for right leg cellulitis. The patient was also taking an ACEI, Lisinopril 40mg daily and Metoprolol 100mg every 8 hours for blood pressure control. Within minutes of arrival to ED, the patient became unresponsive and had to be placed on mechanical ventilation (MV). Vital signs showed blood pressure 70/30 mm/hg and heart rate at 24 bpm. Electrocardiogram (EKG) was performed which showed complete AV node block, and wide QRS with junctional rhythm. Emergent transvenous cardiac pacemaker was placed with improvement in heart rate to 60 bpm. Follow up laboratories showed a serum creatinine level of 5.9 mg/dl and serum potassium (K+) level of 7.5 meq/L. Treatment for severe hyperkalemia was immediately started. The renal service was consulted and emergent hemodialysis was provided for three hours. Both cardiac pacing and mechanical ventilation were discontinued after correction of the hyperkalemia and recovery of cardiopulmonary functions. The patient had recovery of renal function with a returned of serum creatinine to pre-admission levels before he was discharged home.

Case 2

81-years-old man with history of stage 4 CKD secondary to high blood pressure with a baseline serum creatinine level of 4.5 mg/dl. The patient presented to the ED with a complaint of diffuse muscle weakness and nausea. He was prescribed TMP/SMX, two tablets every 12 hours, to be taken for ten days by his primary physician for treatment of urinary tract infection. Laboratory analysis showed severe hyperkalemia with a serum potassium level of 8.3 meq/L. The serum creatinine level had increased to 8.0 mg/dl and the blood urea nitrogen was 109 mg/dl. EKG showed a heart rate at 65 bpm with wide QRS complex. Acute hemodialysis had to be provided for three hours. The serum potassium level normalized after treatment but it took four days for the serum creatinine level to return to baseline. The patient was discharged home.

Case 3

68-year-old man with a history of CKD secondary to diabetes mellitus type II who presented to ED with dizziness for 24 hours followed by an episode of syncope one hour prior to presentation.

Upon evaluation he was found with severe hypotension (60/30 mm/Hg) and bradycardia (24 bpm). EKG was consistent with complete AV node block. Emergent transvenous pacemaker was placed with stabilization of systemic hemodynamics. Laboratories showed a serum potassium level of 7.7 meq/L, and a serum creatinine level of at 5.0 mg/dl and blood urea nitrogen of 100 mg/dl. Medical therapy for hyperkalemia was immediately followed with acute hemodialysis for three. The patient was weaned off the cardiac pacemaker in 12 hours and renal gradually returned to baseline within four days. The patient was also discharged home.

DISCUSSION

In summary, all the patients presented required admission to the intensive care unit and emergency hemodialysis within hours of presentation to the ED. Two of the patients required emergent pacemaker placement due to high degree heart block and one required mechanical ventilation. The three patients were discharged home within few days of admission.

Management of potassium excretion is mainly regulated in the principal cell of cortical collecting duct. The main stimuli for potassium excretion by the distal nephron are tubular fluid flow, the amount of sodium delivered to the principal cell of cortical collecting duct and the aldosterone effect on the same tubular cell. In the principal cell, the epithelial sodium channel (ENaC) activity is regulated by the mineralocorticoid hormone, aldosterone. It increases sodium absorption and potassium secretion in the cortical collecting duct. Reabsoprtion of the positively charge sodium particles creates a net negative charge in tubular lumen. This negative charge promotes movement of potassium from the secreted potassium from the principal cell to the tubular lumen for excretion in urine. Aldosterone also activates the potassium channels in the luminal membrane of the principal cells of the CCD. These cellular effects are essential to maintain potassium balance.

The Renin-Angiotensin-Aldosterone system (RAAS) also plays an important role in potassium handling in the kidney. Angiotensinogen formed in the liver is converted to angiotensin I by the action of angiotensin converting enzyme. Subsequently, angiotensin I is converted to Angiotensin II by angiotensin converting enzyme (ACEI) produced in alveolar epithelium. Angiotensin II then stimulates adrenal cortex to produce the hormone aldosterone that mediates the above-mentioned actions on potassium metabolism. Pharmacologic interruption of the RAAS, with ACEI, ARBs or potassium-sparing diuretics will impair potassium excretion capacity in the kidney, particularly in patients with chronic kidney disease.

Velazquez, et al (1) showed that the Trimetropim component of TMP/SMX inhibits ENaC channel in principal cell. The net negative charge is reduced by up to 66 % in tubular lumen with the blockade of the ENaC thus eliminating the driving force for potassium excretion (2, 3). Studies showed that potassium excretion may fall by as much as 40%. In patients normal renal function with Trimetropim but this seldom produces significant hyperkalemia. However, in patients with chronic kidney disease with an already limited capacity for potassium excretion, life threatening hyperkalemia may develop.

Sprague-Dawley rats with normal kidney function received an intravenous sodium-containing infusion with TMP. Serial urinary potassium excretion measurements were done in control rats with the sodium containing infusion without TMP and in those with TMP. TMP infusion decreased the urinary potassium excretion by 40% when compared to controls (1).
In a study involving thirty consecutive patients with HIV treated with TMP/SMX for presumed pneumocystis carinni pneumonia, the serum potassium level was serially measured. The average increase in serum potassium level during the treatment period was 0.6-1.0 meq/L. In three of the thirty patients (10%), serum potassium levels were higher than 6.0 meq/L. None of the patients were taking NSAIDs, ACEI, or ARBs. There were no patients with significant chronic kidney disease. The average transtubular potassium gradient (TTKG) was 1.9. A value of less than 5 in the setting of hyperkalemia is considered abnormal. This study reiterates that even in the absence of chronic kidney disease, significant hyperkalemia can occur with the use of TMP.

More recently, Weir, et al published a case control study recopilating fourteen years of data on concomitant use of β-blocker and TMP-SMX and the risk of hyperkalemia in elderly patients (4). Two separate cohorts were identified in patients older than 66 years of age. One cohort compared concomitant use of β-blockers with TMP/SMX and the other compared the use of β-blockers with amoxicillin, serving as controls. This database has been previously validated for epidemiologic studies (5). During course of study, hospitalizations for hyperkalemia were identified within fourteen days of filling of the prescriptions for medications. A total of 31,186 prescriptions were filled for concomitant β -blockers and the reference antibiotics. There were 189 hospitalizations for hyperkalemia.

Comorbidities included congestive heart failure in 60% of patients, coronary artery disease in 73 % of patients and chronic kidney disease in 54% of patients. A total of 73% of patients were taking either ACEI or ARB, and 27% were on potassium-sparing diuretics. Analysis of the data showed that patients taking TMP/SMX were five times more likely than controls to develop severe hyperkalemia requiring hospitalization.

The median length of stay for hospitalization was seven days, with a range between four to fourteen days. Seventeen patients (9% of cohort) were admitted directly to the intensive care unit. More significantly twenty-six patients (14% of cohort) died during the hospitalization.

The study did not include cases of mild hyperkalemia that were treated in the ambulatory setting, raising possibility that the total number of patients with hyperkalemia is much higher. This study showed that in the case of concomitant β -blocker, and TMP-SMX administration, the absolute incidence of hyperkalemia was low.

However in the cases where hospitalization was required it carried a significant in-hospitalization mortality of 14 %, with near a 10% requiring admission to the intensive care unit. On the other hand, there is also a higher risk of hyperkalemia with the use of non-selective β1-receptors blocker agents versus β1-selective ones (6, 7).

CONCLUSION

Patients with chronic kidney disease typically have multiple comorbid conditions resulting in significant polypharmacy raising potential for drug interactions. Due to advances in the treatment of arterial hypertension and congestive heart failure with medications that may interfere with the renal potassium excretion, patients with chronic kidney disease are at increased risk of development of clinically significant hyperkalemia. Moreover, great care must be taken in the selection of antibiotic therapy in patients with CKD. If drugs like TMP/SMX need to be use in patients with CKD, the serum potassium level should be monitored not later than three days after starting the medication this will help to indentify the possible development of hyperkalemia. Although severe hyperkalemia with the use of TMP is relatively uncommon; its occurrence may adversely impact the patient's morbidity and the short-term mortality.

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RESUMEN

Reportamos una serie de tres casos de pacientes que desarrollaron hipercalemia severa, la cual puso en peligro su vida, con el uso de un antibiótico de prescripción común, Trimethoprim-Sulfamethoxazole. Los tres pacientes requirieron hemodiálisis de emergencia para normalizar el nivel de potasio en el suero después de desarrollar hipotensión y bloqueo cardiaco por la hiperpotasemia. Todos los pacientes tenían enfermedad renal crónica. Algunos recibían medicamentos que interferían con los efectos de aldosterona. Los pacientes también tuvieron empeoramiento de la función renal durante el episodio de hipercalemia. En estos casos, otras alternativas para la terapia de antibiótico debe de considerarse. Aunque la hipercalemia severa con Trimethoprim es infrecuente, su desarrollo impacta adversamente al paciente y aumentando su mortalidad a corto plazo.

HOPEFUL WAITING: Positive Outcome of Blood Pressure Monitoring in an Emergency Department

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Abstract

Hospitals use a triage system in which health care staff sort's patients into groups. During the long waiting periods after triage, inadvertence of patient's clinical deterioration may occur. Objectives: To determine whether vital signs and oxygen saturation monitoring and reassessment of medical priority during the waiting period had a positive impact on the clinical outcome of apparently non-critical patients. Methods: The study was undertaken in a University Hospital Emergency Department (ED). Patients were sorted into experimental (group A) and control (group B) groups. Temperature, respiratory and pulse rates readings of group A patients were constantly generated by electronic devices and displayed in a computer screen. The results were checked every 5-to-10 minutes. Blood pressure (BP) and oxygen (O2) saturation were verified every 30 minutes. If critical changes occurred, the patient's chart was discretely moved to the top of the waiting pile. Group B patients were not monitored. Clinical outcome (complications, stability of vital signs, and complete resolution of symptoms at discharge) and the length of hospital stay were compared for both groups. Results: Patients in group A had a shorter hospital stay ($p<0.0001$), lower rate of complications ($p=0.003$), and higher rate of vital sign stability ($p<0.0001$) and of complete resolution of symptoms at discharge ($p<0.0001$). Conclusions: Blood pressure monitoring every 30 minutes significantly improved ED waiting patients' clinical outcome and shortened their hospital stay. Observations of oxygen saturation, temperature, pulse, and respiratory rate were not significantly useful.

Index words: *blood, pressure, monitoring, emergency, department*

Introduction

Hospitals usually have a triage system in which health care staff sorts patients into groups based on the perceived need for immediacy of medical treatment according to the severity of illness or injury. [1-4] This sorting process frequently results in long waiting periods and subsequent clinical deterioration in patients with apparently less urgent problems. [1, 2] Although some medical researchers have made suggestions about improving the present triage system,[3, 4] a major drawback continues to revolve around its dependency on vital indicators originally measured by emergency department (ED) staff and not followed sequentially over the waiting period. [5] The absence of recurrent monitoring leads to patient scheduling miscalculations. Therefore, clinical deterioration of patients may occur unnoticed. [6, 7]

The purpose of this study was to determine whether the periodical monitoring of vital signs, and increasing the medical priority of waiting patients with worsening vital indicators, had a positive impact upon their clinical outcome and length of hospital stay.

Methods

The study was carried on in the ED of a University Hospital from December 5th to the 30th of 2009 (11:00 am to 9:00 pm, Saturdays and Sundays were excluded). The exclusion criteria were: (a)-patients younger than 18 or older than 90 years of age; (b)-patients with severely acute or complicated medical conditions who were scheduled for urgent evaluation after the initial triage and who usually arrived to the ED by ambulance; (c)-patients who had skin or muscle diseases that impeded them from wearing the equipment or that could potentially transmit infections by their use; (d)-pregnant women; (e)-patients with pacemakers; and (f)-patients with decompensated psychiatric disorders.

The purpose of the study was then explained to the subjects. Once they signed the required informed consent form, patients were asked their age and date of birth as well as their present and past illnesses. Subsequently, a first set of vital signs data was collected (all vital signs were taken with the same devices at all times and on the same limb, except when verification was needed due to occurrence of critical changes).

Patients were randomized using their day of birth. Patients with even days of birth were sorted into the experimental group (group A) while odd day-of-birth patients were included in the control group (group B). Subjects in group A were asked to wear a chest strap (measuring temperature, heart rate, and respiratory rate), a blood pressure monitor in their left wrists, and a pulse oximeter in one of their fingers. These devices were worn throughout the entire ED waiting period generating continuous readings, which appeared on a computer screen and were checked every 5-to-10 minutes. Blood pressure and oxygen saturation were measured every 30 minutes.

When important changes in vital signs occurred, the patient's medical priority was immediately increased by discretely placing his/her medical record as the next to be taken by the emergency physician (EP) (direct notification to the EP was not done to avoid biasing results). The following specific criteria would lead to placement of the patient's record next in line to be seen by the EP: (a)-blood pressure higher than 170/95 mmHg or lower than 90/60 mmHg; (b)-increase or decrease in diastolic or systolic blood pressure of more than 15 mmHg when compared to the initial level if measurement fell in the abnormal range (higher than 130/85 mmHg or lower than 90/60 mmHg); (c)-heart rate faster than 120 beats per minute (bpm) or slower than 45 bpm; (d)-increase or decrease in heart rate of more than 20 bpm when compared to the initial level if measurement fell in the abnormal range (equal or faster than 100 bpm or equal or slower than 60 bpm); (e)-respiratory rate faster than 25 respirations per minute (rpm) or equal or slower than 10 rpm; (f)-increase or decrease in respiratory rate of more than 10 rpm when compared to the initial level; (g)-body temperature higher than 39.0ºC or lower than 35.0ºC; (h)-increase or decrease in body temperature of more than 2.0ºC when compared to the initial level if measurement fell in the abnormal range (higher than 37.5ºC or lower than 36.0ºC); (i)- oxygen saturation lower than 90%; and (j)-decrease in oxygen saturation of more than 5% when compared to the initial level.

When subjects in group A were called by the EP, the vital signs electronic devices were removed. After experimental and control patients (groups A and B) had the encounter with the EP, their clinical evolution and consultations to specialized services were periodically monitored until discharged, admitted, or transferred. At that point, the final vital signs were measured and feedback about persistence or complete resolution of symptoms was obtained.

The time periods measured were: (a)-waiting time, from patients' arrival to the EP encounter; (b)-physician-evaluation-to-treatment time, from the EP encounter to the moment when treatment was instituted; and (c)-total length of stay, from patients' arrival to the moment he/she left the hospital.

Finally, when hospitalized and/or consulted, subjects' follow-up continued 3-to-5 times a day until discharged. This permitted to assess and compare the clinical outcome of ED waiting patients with periodically monitored temperature, pulse and respiratory rates, and half-hour observations of blood pressure and oxygen saturation after their initial triage with those receiving standard care.

Statistical Analysis: For comparison of categorical variables (number of patients with complications, number of patients with normal vital signs at discharge, and number of patients with complete resolution of symptoms at discharge), 3 steps were utilized. Firstly, Cross-Tabulation Tables (CTT) were elaborated for bivariate analysis. Secondly, depending upon the CTT results, Chi-Square Test of Homogeneity (if CTT result was above 5.00) or Fisher Exact Test (if CTT result was below 5.00) were used for determination of statistical significance of the association (p-value). Finally, Odds Ratio (with a 95% Confidence Interval) was calculated to assess the magnitude of the association (Effect Measures). For comparison of non-categorical or continuous variables (estimated waiting time, physician evaluation-to-treatment time, and total length of stay), medians were analyzed with a non-parametrical test (Mann-Whitney U Test) to determine the statistical significance (p-value) of the medians difference. The local authorities granted internal review board permission for the study.

Results

The study included a total of 92 native Puerto Rican patients: group A was composed of 47 subjects while group B had 45. The demographic distribution of both groups was very equitable (see Figures 1 and 2). A slight predominance of 18-to-40-year-old patients with chronic diseases resulted in both groups as a direct consequence of the exclusion criteria (41-year-old patients or older, particularly those with chronic illnesses, were more prone to arrive by ambulance or with severely decompensated medical problems and were seen promptly). Complaints related to abdomen and lower back prevailed in group A while head, neck, and abdomen were preponderant in group B.

Variables considered to determine clinical outcome were: (a)-complications (hypertensive crisis [emergency or urgency] with heart as target organ, [8-12] hypertensive crisis [emergency or urgency] with Central Nervous System [CNS] as target organ, [8-12] and respiratory distress), (b)-complete resolution of symptoms at discharge, and (c)-normalization of vital signs at discharge (systolic blood pressure equal or lower than 130 mmHg and equal or higher than 90 mmHg, diastolic blood pressure equal or lower than 85 mmHg and equal or higher than 60 mmHg, [8] heart rate slower than 100 bpm and faster than 60 bpm, respiratory rate slower than 20 rpm and faster than 10 rpm, body temperature equal or lower than 37.5 ˚C and equal or higher than 36.0˚C, and oxygen saturation equal or higher than 97.0%).

Monitored patients had less complications (95% confidence interval [CI]: +1.61 to +107.55, $p=0.003$) as well as higher rate of vital sign normalization (95% CI: +2.41 to +14.86, $p<0.0001$) and symptom resolution at discharge (95% CI: +2.60 to +15.96, $p<0.0001$) than non-monitored patients (see Figure 3).

Figure 1. Demographic distribution according to subjects' sex

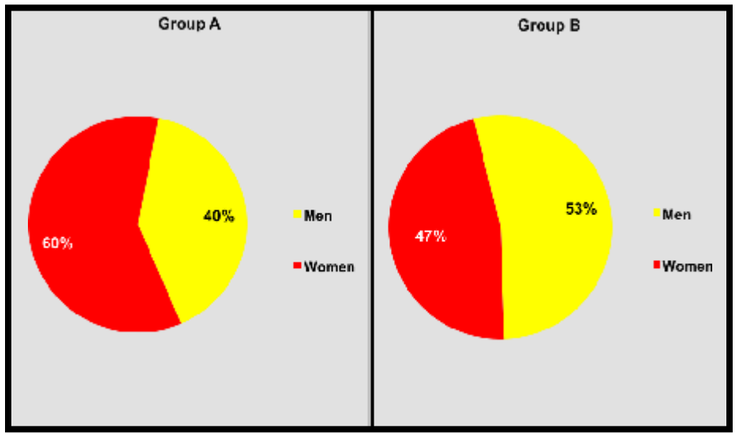


Figure 2. Demographic distribution according to subjects' groups of age.

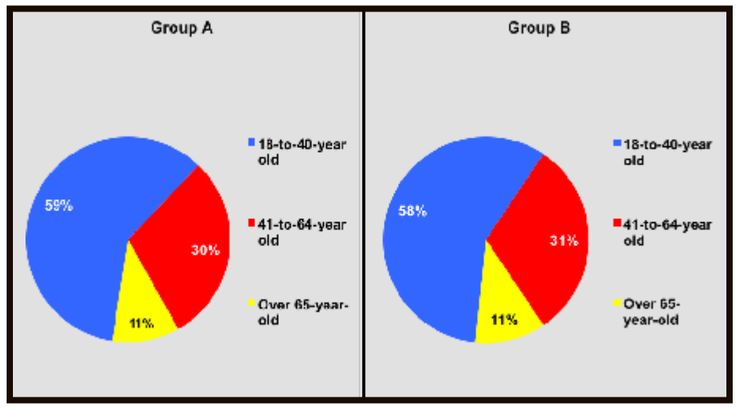
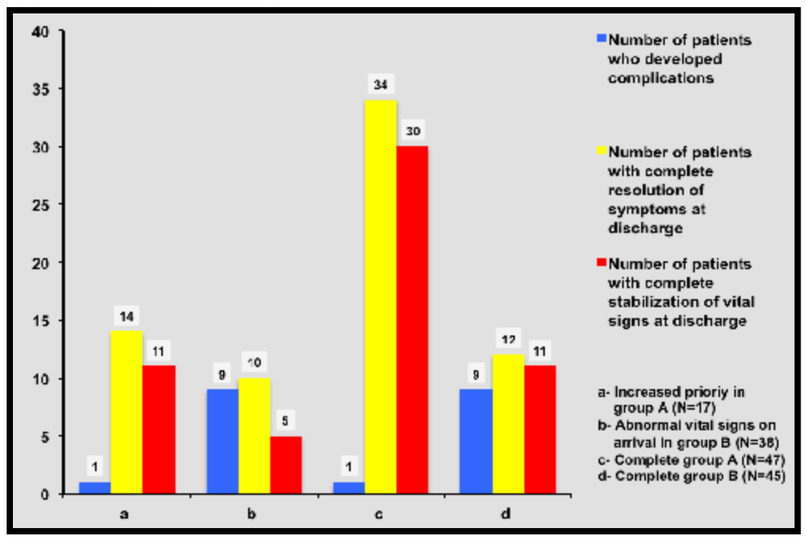


Figure 3. Comparison of global clinical outcome.



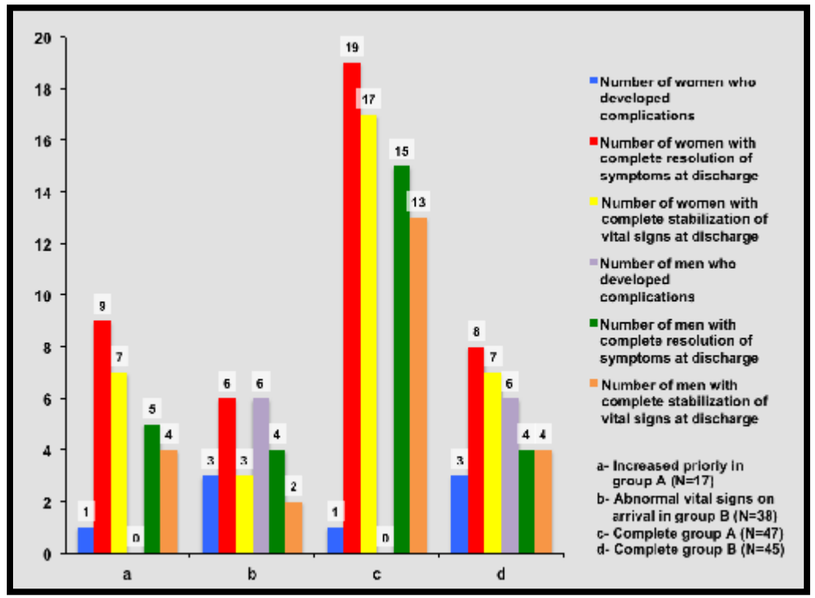
Only 1 (2.1%) patient in group A was presented with heart-as-target-organ-related hypertensive urgency while there were 9 (20.0%) in group B (1 [2.2%] with heart-as-target-organ-related hypertensive emergency, 3 [6.7%] with heart-as-target-organ-related hypertensive urgencies, 4 [8.9%] with CNS-as-target-organ-related hypertensive urgencies, and 1 [2.2%] with respiratory distress). Thirty (63.8%) patients in group A but only 11 (24.4%) in group B had completely normal vital signs at discharge. Total resolution of symptoms at discharge was also more frequent in group A (34 [72.3%]) than in group B (12 [26.7%]).

Globally, men fared worse than women (see Figure 4). However, those in group A were clinically better at discharge (0 complications, 13 [27.7%] with normal vital signs, and 15 [31.9%] with no symptoms) than those in group B (6 [13.3%] with complications, 4 [8.9%] with normal vital signs, and 4 [8.9%] with no symptoms).

When comparing the clinical outcome of patients in group A whose medical priority was increased (17 [36.2%] patients) with those in group B with abnormal vital signs on arrival (38 [84.4%] patients) (see Figure 4), again, the ones in group A had much better results than those in group B. Although there was no significant difference when comparing the number of complications, a positive tendency favored group A patients. These patients had 1 (5.9%) complication while group B resulted with 9 (23.7%). Eleven (64.7%) group A patients had complete normalization of vital signs at discharge while group B had only 5 (13.2%) (95% CI: +3.89 to +64.54, p<0.0001). Finally, 14 (82.4%) group A patients had a total resolution of symptoms at discharge versus 10 (26.3%) in group B (95% CI: +2.74 to +47.89, p<0.0001).

Interestingly, among all vital signs and oxygen saturation, 30-minute-interval-monitoring of blood pressure resulted in the most useful and consistent indicator of a need for a priority change. Body temperature was the least important. Thirteen out of the 17 increased-priority group A patients (76.5%) had critical changes in blood pressure and only 1 (6.0%) needed his priority increased due to important changes in temperature.

Figure 4. Comparison of clinical outcome according to subjects' sex.



Group A patients whose medical priority was not increased (30 [63.8%]) had also a significantly improved outcome when compared with those in the entire group B. They developed no complications (p=0.005 by Fisher Exact Test), and at discharge, 63.3% (19 patients) had normal vital signs (95% CI: +1.95 to +14.61, p=0.002), and 66.7% (20 patients) had complete resolution of symptoms (95% CI: +1.82 to +13.33, p=0.002).

Total length of stay for all non-monitored patients was longer (11.0 h) than those in complete group A (3.6 h; p<0.0001), those with increased priority in group A (3.9 h; p<0.0001), and those in group A whose medical priority was not increased (3.4 h; p<0.0001). Likewise, abnormal-vital-signs-on-arrival group B patients spent more time in the hospital (12.0 h) than those in complete group A (3.6 h; p<0.0001), increased-priority group A patients (3.9 h; p<0.0001), and those without increased priority in group A (3.4 h; p<0.0001). Although waiting time and physician-evaluation-to-treatment time had a tendency to be shorter in group A, no statistical significance was found.

Consultations to specialized services were requested for two patients, 1 from group A (to Orthopedics) and 1 from group B (to Internal Medicine and Surgery). Only 1 admission (to Internal Medicine ward) from group B occurred due to unstable angina pectoris, complicated diabetic foot, and uncontrolled type 2 diabetes mellitus. This patient remained in the hospital for 9 days, 23 hours and 35 minutes and was finally transferred to a cardiovascular center for percutaneous transluminal intervention. None of the group A patients were admitted to the hospital.

Discussion

Present triage system's fails to promptly detect patients' vital signs changes and clinical status deterioration d uring ED waiting time. This has led to new ideas, including vital signs monitoring.[6, 7, 13, 14] Despite that, medical literature investigating clinical outcome of ED waiting patients managed with priority change due to critical vital signs variations was not found. Periodical blood pressure monitoring in patients waiting in the ED may detect critical changes that should prompt urgent medical management to avoid further decompensation.

Had group A patients been managed conventionally (as group B patients were), the necessity to increase medical priority would have been unnoticed and clinical outcome would have been poorer, as occurred with those in group B.

Interestingly, patients in group A whose medical priority was not increased also had a better outcome. Human well-being is based upon an inseparable and healthy relationship between his/her biological, psychological, and social components. [15, 16] Therefore, patient treatment priority embraces a dynamic concept that varies in time depending on many psychosomatic and/or organic variables whose fluctuation in intensity may lead to alterations in vital signs and poor final outcome. [17-25] It has been shown that while waiting in an ED, a heightened physiologic response and elevated catecholamine levels (particularly: norepinephrine and serotonin [26, 27]) supervene as a direct consequence of patient's pain, anxiety, lack of information, and feelings of helplessness, distrust, and fear. [28, 29] For several decades, it has been demonstrated that such effects, particularly in those with chronic cardiovascular and pulmonary diseases, may strongly induce gradual deterioration and occurrence of serious cardiopulmonary and neurological complications. [8-12, 30] This may negatively affect clinical outcome if not managed expeditiously. The patient's perception of constant care through continuous monitoring may have ameliorated the sensation of fear and abandonment, as well as the anxiety-related catecholamine surge effect that the chaotic ED environment provokes. [28, 29]

In order to draw reliable conclusions about the effect of our intervention, assessment of patients' clinical outcome encompassed both the objective and subjective spheres by measuring medical complications, normalization of vital signs at discharge, and complete resolution of symptoms at discharge. Those three variables had significantly better results in a shorter time for the experimental group patients (group A), therefore, we may state that our intervention (particularly 30-minute-interval blood pressure monitoring) favorably aided their stabilization. Since blood pressure monitoring

every 30 minutes was the leading indicator that led us to promptly detect patients' increasing medical need, we may conclude that periodic measurement of blood pressure alone is a reasonable strategy for improving the clinical outcome of patients who wait in the ED. This is a simple and affordable intervention.

Conclusions

Observations every 30 minutes of oxygen saturation and 5-to-10-minute-interval of temperature, pulse, and respiratory rate in emergency department waiting patients do not yield useful information for prompting an increase in their medical priority. However, blood pressure monitoring every 30 minutes significantly improves these patients' clinical outcome and shortened their hospital stay. This approach is simple, and inexpensive. It is certainly a readily implementable task in any emergency department.

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RESUMEN

Los hospitales han creado un sistema de sorteo (triage en inglés) a través del cual el personal de cuidado médico clasifica los pacientes en grupos. Durante los largos períodos de espera después del proceso de sorteo, el deterioro clínico de los pacientes puede ocurrir de una manera inadvertida. Objetivos: Determinar si el monitoreo de signos vitales y saturación de oxígeno arterial, así como la reevaluación de la prioridad médica durante el período de espera tenían un impacto positivo en el desenlace clínico de los pacientes que aparentemente no estaban en un estadio crítico. Métodos: El estudio se realizó en la Sala de Emergencias (SE) de un hospital universitario. Los pacientes se sortearon en dos grupos: experimental (grupo A) y control (grupo B). Las lecturas de la temperatura corporal así como de las frecuencias respiratoria y cardíaca de los pacientes del grupo A se generaron constantemente mediante aditamentos electrónicos y se mostraban en la pantalla de un monitor computarizado. Los resultados se verificaron cada 5 a 10 minutos. La presión arterial y la saturación arterial de oxígeno se midieron cada 30 minutos. Si ocurrían cambios críticos, el expediente del paciente se colocaba discretamente en el primer lugar del conjunto de expedientes en espera. Los pacientes del grupo B no se monitorearon. Se comparó el desenlace clínico (complicaciones, estabilidad de los signos vitales y resolución completa de la sintomatología al momento del alta) y la estadía total intrahospitalaria para ambos grupos. Resultados: Los pacientes del grupo A tuvieron una estadía intrahospitalaria más corta ($p<0.0001$), una menor taza de complicaciones ($p=0.003$), y una mayor taza de estabilidad de signos vitales ($p<0.0001$) y de resolución completa de la sintomatología ($p<0.0001$) al momento del alta. Conclusiones: El monitoreo de la presión arterial cada 30 minutos mejoró significativamente el desenlace clínico de los pacientes que esperaban en la SE y acortó el tiempo total de estadía intrahospitalaria. Las observaciones de la saturación de oxigeno, temperatura corporal, y las frecuencias respiratoria y cardíaca no arrojaron resultados significativamente útiles.

KIDNEY BIOPSY FINDINGS AS PROGNOSTIC FACTORS OF RENAL OUTCOME IN A CASE OF ANCA-ASSOCIATED GLOMERULONEPHRITIS

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ABSTRACT

We present the case of a 29-year-old woman with twelve-years history of Wegener's granulomatosis and multiple relapses resulting in chronic kidney disease. The patient was referred to our center for kidney biopsy, after presenting with a relapse of Wegener's disease mainly manifested by rapid progressive glomerulonephritis. Kidney biopsy was obtained and she was treated with intravenous methylprednisolone and oral cyclophosphamide as initial therapy. Histopatological findings are described, followed by a discussion on how it can be used as a tool to established renal prognosis.

Index words: *kidney, biopsy, prognosis, outcome, ANCA, glomerulonephritis*

CASE PRESENTATION

This is the case of a 29-year-old Hispanic woman with history of Wegener's granulomatosis diagnosed at age 19 years. Her symptoms started two years prior diagnosis with arthritis, fever, anemia, proteinuria and skin lesions. At the time of diagnosis she had a positive antineutrophilic cytoplasm antibody (ANCA) and a kidney biopsy revealed findings compatible with Wegener's vasculitis.

Initial treatment consisted of oral cyclophosphamide and high dose glucocorticoid followed by maintenance therapy with oral azathioprine, after which she went into remission for two years. Several disease flares, causing her to develop chronic kidney disease, characterized her disease course. The most remarkable disease exacerbation occurred in 2003, manifested by pulmonary cavitary lesions and Mycobacterium kansasii colonization, at that time requiring pulse glucocorticoid therapy, oral cyclophosphamide and antibiotics.

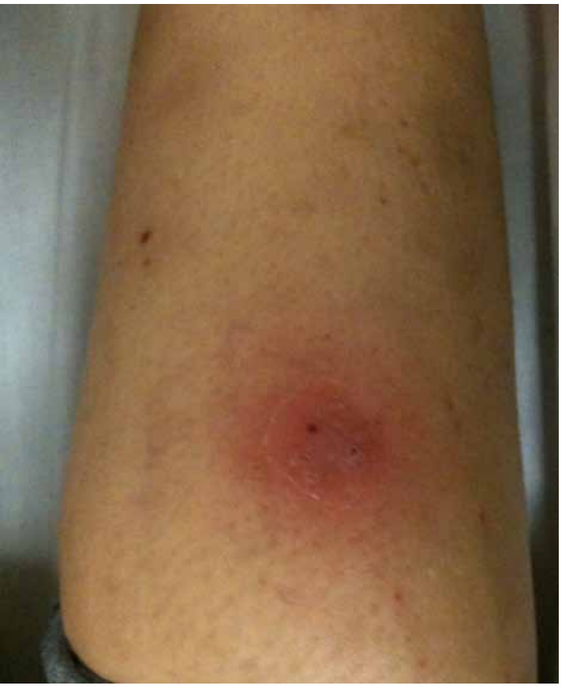
She presented to our Nephrology Center referred by her primary nephrologist due to acute deterioration of kidney function (increased serum creatinine from 2.5 mg/dL to 3.9 mg/dL), associated with hematuria, palpable purpura and skin nodules. She denied fever, weight loss, visual symptoms, cough, hemoptysis or arthralgia, but two weeks ago had an episode of gastrointestinal bleeding manifested as melena.

Her usual medication included azathioprine 100 mg/day, prednisone 20 mg/day, enalapril 10 mg twice a day and ranitidine 300 mg/day. She denied any toxic habits, but her family history was remarkable for several cases of rheumatoid arthritis and systemic lupus erythematosus from maternal side.

Upon arrival to our institution, examination revealed stable vital signs, full-moon fascies, bluish scleras, abdominal striaes, vasculitic rash and nodules over upper and lower extremities (see Figure 1). Initial blood test showed anemia with a hemoglobin of 9.2 g/dL, significant renal impairment with a serum creatinine of 4.68 mg/dL, and ongoing inflammatory response with sedimentation rate (ESR) 80 mm/hr and C-reactive protein (CRP) 2.110 mg/dL (see Table 1). Urinalysis demonstrated blood and protein on dipstick testing, urine microscopy showed many red blood cells (> 50/mL); also ANCA was positive on a cytoplasmic pattern. Chest radiograph showed a nodular density in the right lung laterally measuring 1.5 x 1.85 cm and several nodularities in the left base (see Figure 2); this was followed by a high resolution chest computer tomography (CT) without the administration of intravenous contrast, that demonstrated bilateral small cavitary nodules and a solid nodule in the right upper lobe (see Figure 3).

In preparation for kidney biopsy a renal ultrasound was done, showing increased cortical echogenicity bilaterally and decreased size of the right kidney (8.2 cm long x 4.6 cm AP) as compared to left kidney (10.5 cm long x 5.2 cm AP). A clinical diagnosis of rapid progressive glomerulonephritis secondary to Wegener's granulomatosis reactivation was made. The patient was hydrated with isotonic saline solution and started on pulse methylprednisolone 1 g intravenous daily for three days; also percutaneous kidney biopsy was done without complication. While waiting for biopsy results inductive therapy was continued with oral

Figure 1: Right leg pretibial erythema nodosum and antecubital fossa rash.



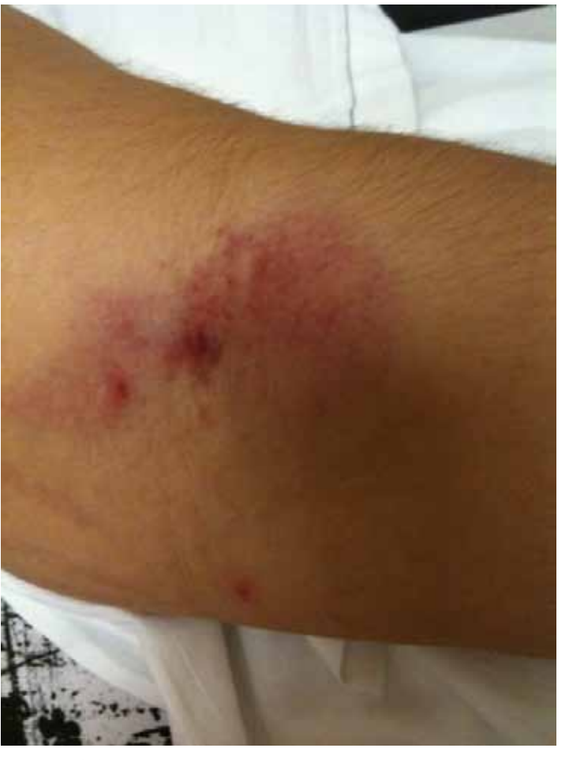


Figure 2.Chest radiograph shows multiples ill defined nodularities more prominent in the right lung periphery and left lung base.

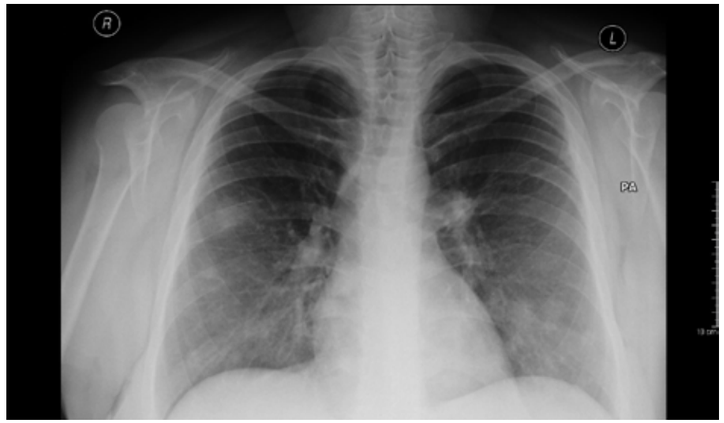
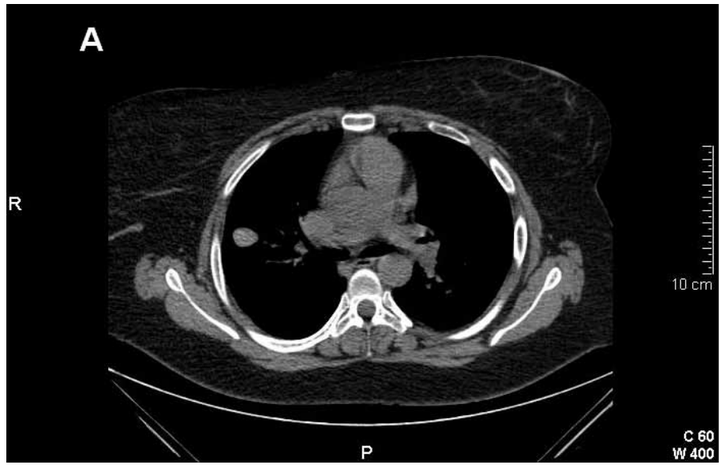


Figure 3. High resolution computer tomography of the chest shows round pulmonary nodule measuring 1.8 cm AP by 2.2 cm transverse at the posterior segment of the right upper lobe (A) and multiple small cavitary nodules on lower lobes (B).



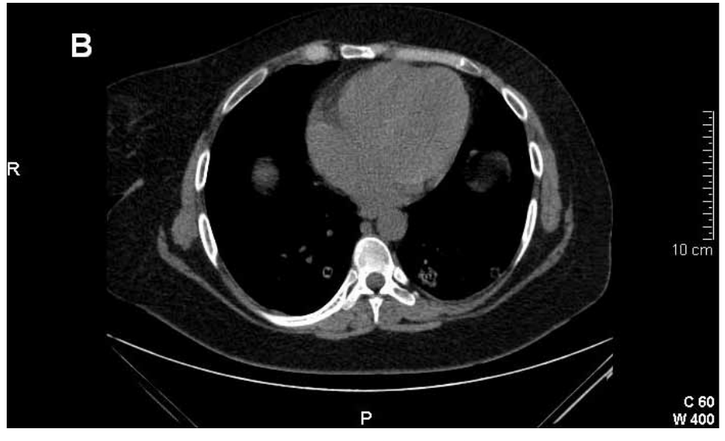
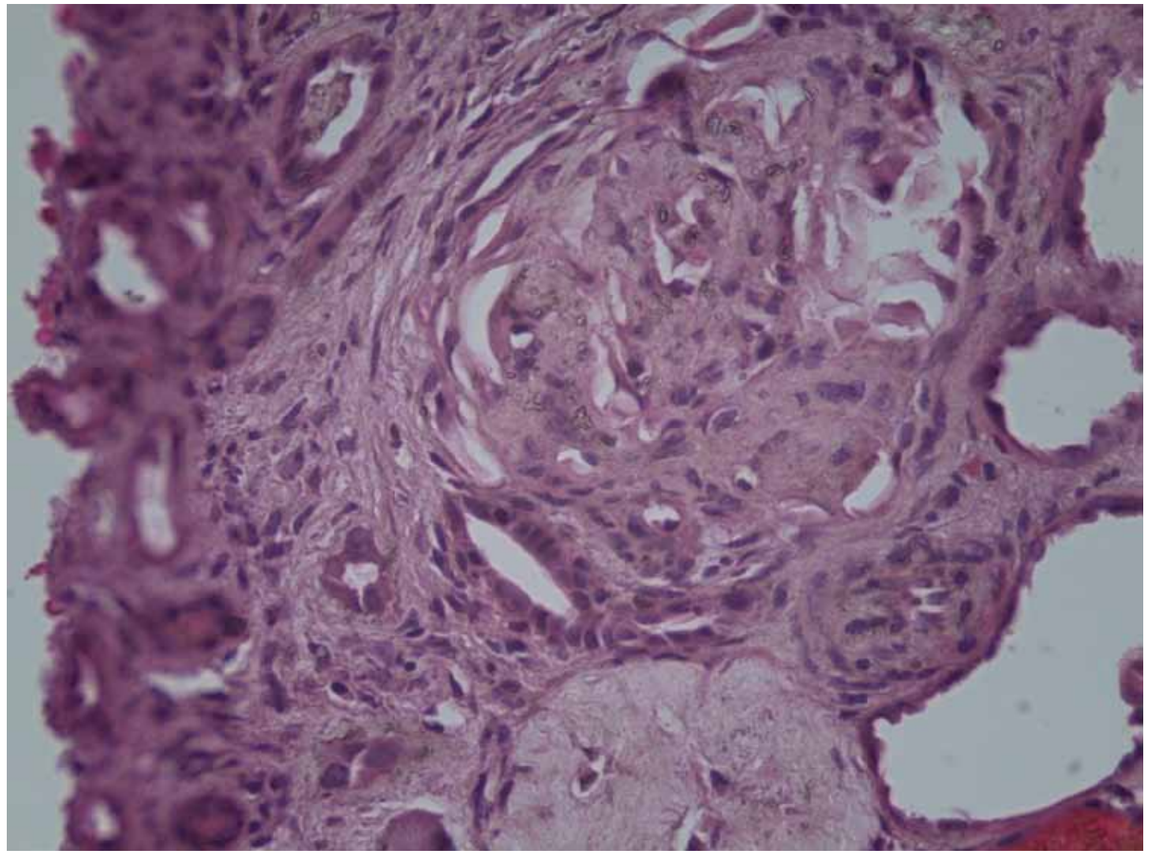


Figure 4. Kidney biopsy on light microscopy (hematoxylin and eosin staining) shows a sclerotic glomeruli and atrophic tubular epithelium with interstitial fibrosis.



cyclophosphamide (2mg/kg) plus oral prednisolone (1 mg/kg/day).

After starting intravenous pulse methylprednisolone her serum creatinine started to decrease, her urine output kept stable, and on ninth day was discharged home with a serum creatinine of 3.24 mg/dL. No intrahospital complications occurred.

RENAL BIOPSY RESULT

Renal cortical tissue disclosed twenty glomeruli with global sclerosis, and three with focal sclerosis (see Figure 4). Tubules disclosed granular cast, and abundant RBC's casts, fibrotic interstitium with lymphocytic infiltrate; but no evidence of vasculitis on blood vessels. Immunofluorescence showed scanty mesangial IgG and IgA. No electrodense deposits were seen. The diagnosis was chronic glomerulonephritis, global and focal sclerosis of twenty-two out of twenty eight glomeruli (82%), with no evidence of vasculitis.

DISCUSSION

Wegener's granulomatosis, microscopic polyangitis , and Churg Strauss syndrome are classified as small vessel vasculitis according to the Chapel Hill Consensus Conference (1), and are associated with the presence of antineutophil cytoplasm antibodies (ANCA) (2). The incidence of these diseases is increasing, with more than 20 per million affected and occurring more often in the elderly (3). The median age at presentation is between 55 and 65 years in the majority of studies with large cohorts of patients, genders were equally distributed (4). In Puerto Rico there are no epidemiologic data regarding incidence, prevalence and distribution of the ANCA associated vasculitis (AAV). Here we present an unusual case of Wegener's granulomatosis, presenting with renal involvement at a very young age.

Wegener's granulomatosis usually manifest by a wide variety of signs and symptoms reflecting multiorgan involvement; including constitutional symptoms like fever, anorexia, weight loss and myalgia. Ocular disease with proptosis, uveitis, episcleritis, and optic neuritis. Upper respiratory tract compromise is manifested by nasal congestion, rinorrhea, epistaxis, sinusitis, collapse of nasal bridge (saddle nose) and tracheal stenosis. Lung involvement is very common and can be life threatening requiring high diagnostic suspicion; it can

presents with cough, dyspnea, hemoptysis and pulmonary hemorrhage. Gastrointestinal tract, heart and peripheral nerves can also be compromised, causing gastrointestinal bleeding, myocardial ischemia and mononeuritis multiplex, respectively. The renal manifestations include oliguria, microscopic hematuria, proteinuria, red cell cast and impaired glomerular filtration rate manifested as increased serum creatinine (5).

Despite the presence of clinical features of a rapid progressive glomerulonephritis and positive ANCA, a definitive diagnosis cannot be established without a kidney biopsy, which remains to be the gold standard. In the literature there has been previous description of recurrent renal failure after treated ANCA associated vasculitis, which resulted to be biopsy proven cases of interstitial nephritis secondary to azathioprine used for maintenance therapy (6, 7). Histologically the AAV is characterized by a pauci-immune (minimal or absent staining for immunoglobulin or complement on immunofluorescent microscope) staining pattern, focal segmental necrotizing glomerulonephritis that may become crescentic with the accumulation of macrophages and epithelial cells in Bowman's space (light microscopy) and lack of electrodense deposits (8, 9).

Our patient presented with active skin lesions compatible with vasculitis and recent gastrointestinal bleeding possibly reflecting intestinal ischemia, as well as, rapid and continuous deterioration of kidney function (increased baseline serum creatinine from 2.5 mg/dL to 4.6 mg/dL at presentation), associated to active urine sediment. She was immediately started on pulse methylprednisolone and oral cyclosphospamide to avoid progression to ESRD. Kidney biopsy was done to establish diagnosis and guide therapy, based on histological findings. Unfortunately biopsy showed a chronic glomerulonephritis with sclerotic pattern, which confers her a poor renal prognosis, despite partially regression of serum creatinine levels to a new baseline of 3.4 mg/dl, with an estimated glomerular filtration rate (GFR) of 17 ml/min/1.73m2 by Modification of Diet in Renal disease formula (MDRD) (10). This kidney pathology finding reflects the chronic relapsing nature of this disorder, which promotes the accumulation of healing scars.

Increased age, creatinine level at presentation and chronic lesions on renal biopsy are all associated with worse renal outcome for renal recovery, progression to end stage renal disease (ESRD), and death (11). In search for histopathologic prognostic factors several studies has been conducted, showing that some specific pathologic lesions like percentage of globally sclerotic glomeruli (12, 13) and tubular atrophy (14) are risk factors for adverse renal outcome. Instead, active crescentic lesions can be seen in patients with subsequent renal recovery (12).

More recently, Berden, et al (15) developed a pathologic classification based on glomerular characteristic as assessed on light microscopy. This classification includes four categories: Focal (≥ 50% normal glomeruli), crescentic (≥ 50% glomeruli with cellular crescents), sclerotic (≥ 50% glomerular with global sclerosis) and mixed (<50% normal, < 50% crescentic, <50% globally sclerotic glomeruli). They correlated biopsy category to the degree of renal function at presentation and at one and 5 years follow up. Multiple regression analysis showed that the percentage of patients who developed ESRD increases with ascending category, in the following order: focal, crescentic, mixed and sclerotic. In the survival analysis, they illustrated that patients with. sclerotic ANCA-associated glomerulonephritis not only have worse renal prognosis, but also are at higher risk for death

All the above mentioned clinico-pathological associations emphasize the importance of obtaining kidney biopsy in all cases of ANCA-associated glomerulonephritis, not only to establish a proper diagnosis, but also to help guide therapy based on prognostic factors.

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RESUMEN

Presentamos el caso de una mujer de 29 años de edad con historial de granulomatosis de Wegener's desde los 17 años de edad, caracterizada por varias reactivaciones lo que la lleva a padecer de enfermedad renal crónica. La paciente presenta con una nueva reactivación de su enfermedad, manifestada principalmente como una glomerulonefritis rápidamente progresiva; por lo que es referida a nuestro centro para una biopsia renal. Ella es tratada inmediatamente con metilprednisolona intravenosa y ciclofosfamida oral como terapia de inducción. Seguido desglosamos el resultado de la biopsia renal y describimos como estos hallazgos pueden ser usados como una herramienta para establecer el pronóstico renal.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A rare acquired hematologic disorder

ABSTRACT

Paroxysmal nocturnal hemoglobinuria is a rare hematological disorder. It is an uncommon cause of intravascular hemolysis, thrombosis and bone marrow suppression. We report a 19-year-old female patient admitted to the hospital with pancytopenia. Workout of pancytopenia disclosed paroxysmal nocturnal hemoglobinuria. The patient responded well to treatment with blood transfusions, steroids and eculizumab. We discuss the underlying pathophysiology, clinical manifestations and treatment of this rare entity.

Index Words: *paroxysmal, nocturnal, hemoglobinuria, hematology, disorder*

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria is a clonal, hematopoietic stem cell disorder that results in the formation of defective red cells, white cells and platelets [1]. Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon, acquired stem cell disorder characterized by defective hematopoiesis, which results in an increased sensitivity of the erythrocytes to complement mediated intravascular hemolysis [2]. The patients with PNH present dark urine at night that is distinctive and easily observed. The pigment is confirmed to be hemoglobin due to hemolysis of red cells. The clinical manifestations are mainly related to hemolytic anemia, hypercoagulable state and bone marrow aplasia. The diagnosis is extremely complex and requires high level of clinical suspicion. PNH often goes unrecognized by physicians, with delays in diagnosis ranging from approximately from one to more than 10 years. In this case report, we present a case of 19-year-old female patient with poorly explained pancytopenia who was finally diagnosed as PNH. Paroxysmal nocturnal hemoglobinuria should be considered by the physicians when evaluating a young adult patient with pancytopenia and clinical manifestations of intravascular hemolysis.

Case History

A 19-year-old female patient G1 P1 A0 came to the emergency room complaining of weakness and dizziness of five days of evolution. The patient presented her menstrual period for five days but denied any rectal bleeding episode. The physical exam was remarkable for an acutely ill patient, with pale conjunctiva and appearance. The laboratory showed the white blood cells 2.20 K/ul (N = 4.60-10.20 K/uL), hemoglobin level 5.60 g/dl (N = 12.20-18.10g/dl), hematocrit 17.40% (N = 37.70-53.70%), platelet 110.00 K/ul (N = 142.00-424.00 k/ul), MCV 82.86 FL (N = 80.0-97.00 FL), MCH 26.67 PG (N = 27.00-31.00 PG), MCHC 32.18% (N = 31.80-35.40%). The serum B-HCG was negative; PT 11.1 (N = 9.6-12.2 sec), INR 1.0 (N = 0.8-1.10) and PTT 30.7 sec (N = 25.0-35.0 sec). The total bilirubin was 4.8 mg/dl (N = 0.1-1.4 mg/dl), direct bilirubin less than 0.2 mg/dl (N = 0.0-0.3 mg/dl), the indirect bilirubin 5.1 mg/dl (N = 0.0-1.1 mg/dl) and LDH 4,424 U/L (N = 313-618 U/L). The patient was admitted with a diagnosis of pancytopenia, symptomatic anemia and menorrhagia. The patient was transfused with 3 units of PRBC. An abdominal sonogram was remarkable for mild splenomegaly with a splenic span of 12.4 cm. The chest x-ray revealed no active lung disease. The stool occult blood test was negative. An hepatitis profile and HIV were non-reactive. The ANA test was negative. An hemoglobin electrophoresis was normal. A bleeding time was 2 min. with 30 sec (N = 1.0-3.0 min.). The chest/abdominal/pelvis CT scans were normal. Finally a bone marrow biopsy was performed. The bone marrow cytogenetic analysis revealed normal female karyotype 46, XX without apparent clonal aberrations. The hematopathology report of the bone marrow aspirate, core biopsy and clot specimen showed cellular bone marrow with trilineage hematopoiesis, increased erythropoiesis, decreased storage iron and no significant increase in blasts. The bone marrow flow cytometry report revealed no increase in blasts and no significant immunophenotypic abnormalities. The final diagnosis of the bone marrow revealed a normocellular bone marrow with erythroid hyperplasia, decreased storage iron, no evidence of leukemia and no cytogenetic abnormalities in favor of reactive process. The morphology of the peripheral blood demonstrated a mild normocytic, hypochromic anemia, leukopenia with neutropenia and thrombocytopenia. In view that the patient continued presenting clinical manifestations of pancytopenia and intravascular hemolysis the decision was to perform a peripheral flow cytometry for the suspicion of PNH.

The peripheral blood flow cytometry showed populations with deficient or absent GPI-anchored proteins CD55/CD59/CD14 expression [see Figure 1]. The flow cytometry of the peripheral blood identified a population with deficient or absent levels of expression of glycosylphosphaditylinositol linked antigens and anchor proteins on 19.7% of erythrocytes, 47% of granulocytes and 43% of monocytes consistent with a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) [see Figure 1 and 2]. The patient was started in prednisone 40 mg PO daily and eculizumab (soliris) 600 mg IV weekly for 4 weeks followed by 900 mg IV every 14 days. The prednisone eventually was tapered down to 10 mg PO daily. Eventually the laboratories showed a significant reduction in the destruction of red blood cells, reduced platelet consumption following eculizumab and corticosteroid treatments [see Figure 3].

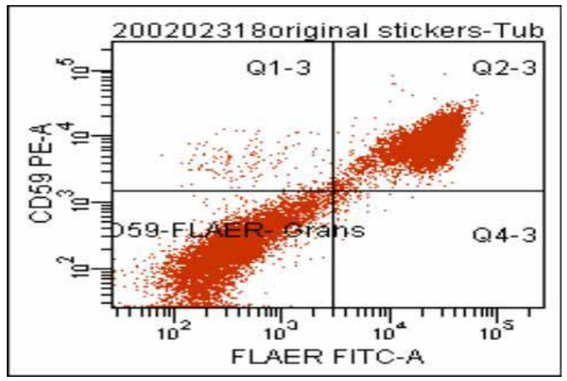

Figure 1: Population of deficient or absent GPI anchor protein in 47% of granulocytes showing lack of staining with both anti-CD59/CD55 and FLAER (Fluorescein-labeled proaerolysin). The flow cytometry analysis was performed using antibodies to GPI-linked antigens CD14, CD55 and CD59 and FLAER.

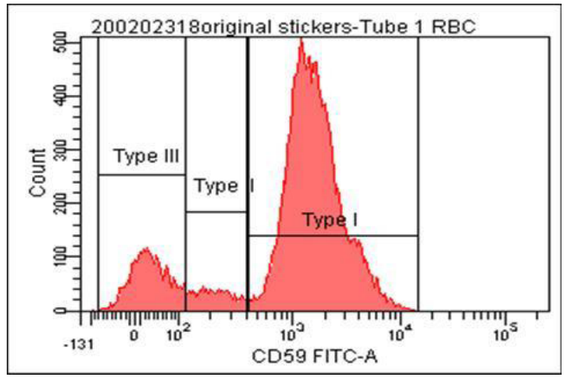

Figure 2: Peripheral blood flow cytometry for PNH showed populations with deficient GPI-anchored proteins. The RBC showed Type I normal expression CD55/CD59 in 80.3%, Type II deficient CD55/CD59 expression in 5.5% and Type III absent CD55/CD59 expression in 14.2% of total RBC's.

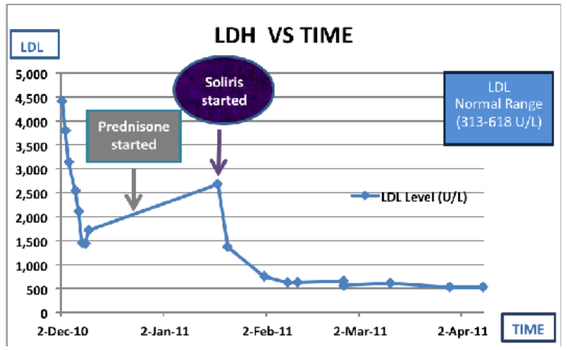

Figure 3: Reduction in intravascular hemolysis during treatment with eculizumab. Levels of lactate dehydrogenase reflect the degree of hemolysis from december to april. The level of lactate dehydrogenase was rapidly reduced to the normal range after eculizumab began.

DISCUSSION

Paroxysmal nocturnal hemoglobinuria is a rare, acquired myelodysplastic stem cell disorder [2]. This condition affects all three hematopoietic lines [2]. Paroxysmal nocturnal hemoglobinuria (PNH) is a consequence of non-malignant clonal expansion of one or several hematopoietic stem cells that have acquired a somatic mutation of phosphatidylinositol glycan-class A (PIG-A) gene leading to deficient glycosyl phosphatidylinositol (GPI)-anchored proteins synthesis [3]. The pathophysiology of PNH is an abnormality in the glycolipid-anchored proteins of the membranes of blood cells [3]. The absence of complement control proteins, including decay accelerating factor (DAF, CD55) and membrane inhibitor of reactive lysis (MIRL, CD59), results in intravascular lysis of the abnormal cells [3]. Molecular studies revealed the absence of GPI anchor proteins, which binds several proteins to the cell membrane, due to an abnormality in the PIG-A gene [1]. Such proteins, which include leukocyte alkaline phosphatase, acetyl cholinesterase, decay accelerating factor-DAF (also called CD55), membrane attack complex inhibitory factor (also known as CD59) and many other deficient proteins of unknown significance [1]. Glycosyl phosphatidylinositol-anchored proteins (GPI) consists of two molecules, phosphatidylinositol (PI) that is inserted into the cell plasma membrane and a molecule of ethanolamine (ETN) that binds to the protein molecule [1]. Both CD55 and CD59 protect red cells from the lytic action of activated complements [1]. Deficiency of CD55 and CD59 lead to the increased sensitivity of red cells and platelets to complement, with resultant hemolysis and thrombosis, respectively [1].

The PNH originates from a multipotent hematopoietic stem cell that acquires a mutation of the PIG-A gene [12]. Expansion and differentiation of the PIG-A mutant stem cell lead to clinical manifestations of the disease. The PIG-A gene product is required for the biosynthesis of glycophosphatidylinositol anchors proteins, a glycolipid moiety that attaches dozens of proteins to the plasma membrane of cells [12].

Consequently, the PNH stem cell and all of its progeny have a reduction or absence of glycosyl phosphatidylinositol (GPI) anchored proteins [12]. Two of these proteins, CD55 and CD59, are complement regulatory proteins; the absence of these proteins is fundamental to the pathophysiology of the disease [12]. CD55 inhibits C3 convertases and CD59 blocks formation of the membrane attack complex (MAC) by inhibiting incorporation of C9 into the MAC [12]. The loss of these complement regulatory proteins renders PNH erythrocytes susceptible to both intravascular and extravascular hemolysis, but it is the intravascular hemolysis that contributes too much of the morbidity and mortality from the disease [12]. Intravascular hemolysis releases free hemoglobin into the plasma [12]. Free plasma hemoglobin scavenges nitric oxide and depletion of nitric oxide at the tissue level contributes to numerous PNH manifestations, including esophageal spasm, male erectile dysfunction, renal insufficiency and thrombosis [12].

Factors reported as precipitating hemolysis in this patients include infections, drugs, exercise, transfusions, surgery but the cause often remains unknown [2]. The clinical course of PNH is very variable [2]. Moreover, these patients can exhibit a wide range of manifestations including bone marrow hypoplasia, venous thrombosis and increased sensitivity to infections [2]. Tendency for thrombosis is markedly increased in PNH patients. It is mainly at unusual sites, such as hepatic vein, portal or splenic veins, cerebral veins or other veins [1]. Hepatic venous thrombosis and cerebral vein thrombosis are more sinister complications causing deaths in the PNH patients. The venous thrombosis may involve almost any organ or site and is the leading cause of death [3]. The portal, superior, and inferior mesenteric and splenic veins are the common abdominal sites of thrombosis [8]. Budd-Chiari Syndrome, an obstruction of hepatic venous outflow at any level of the small hepatic veins to the junction of the inferior vena cava and the right atrium occurs with moderate frequency in patients with PNH [8]. In our patient, we did not detect any venous thrombosis episodes, even with her pregnancy that predisposes to this complication.

PNH can produce chronic renal failure caused by hemosiderin deposition in the proximal convoluted tubules in the renal cortex and repeated microinfarctions occur due to microvascular thrombosis or a direct nephrotoxic effect of iron [2]. Hemoglobinuria and hemosiderinuria are present and may eventually lead to iron deficiency anemia and renal failure [1]. The major clinical manifestations of PNH are paroxysmal hemolytic anemia, venous thrombosis, and diminished hematopoiesis, which can lead to cytopenias or aplastic anemia [1]. Anemia seen in PNH may be severe enough to warrant blood transfusion as seen in our patient who received blood transfusion three times during her admission. The clinical course of PNH is usually chronic and survival ranges from a few months to many years (median of approximate 10 years) [3]. It is estimated that approximately one-third of patients with PNH do not survive more than five years from the time of diagnosis [7]. PNH is a rare blood disorder that affects people of all ages, with an average age of onset in the early 30s [5]. Approximately 10 percent of all patients first develop symptoms at 21 years of age or younger [6]. The diagnosis is confirmed by the Ham acid hemolysis test [1]. Sucrose test is less sensitive and specific. Recently, the expression of GPI anchored proteins on hematopoietic cells can be analyzed by a simple method using monoclonal antibodies and flow cytometry with increased sensitivity and specificity [1]. Ideally, at least 2 different monoclonal antibodies, directed against 2 different GPI-anchored proteins, on at least 2 different cell lineages should be used to diagnose a patient with PNH. Solely screening red cells for PNH can lead to falsely negative tests, especially in the setting of a recent hemolytic episode or a recent blood transfusion. Because granulocytes and monocytes have a short half-life and are not affected by blood transfusions, the percentage of PNH cells in these lineages best reflects the size of the PNH clone [12]. Quantification of serum LDH is particularly informative because intravascular hemolysis results in markedly elevated values. Multiple proteins were found to be deficient in PNH cells besides CD55 and CD59. These are urokinase receptor [CD87], endotoxin binding protein receptor [CD14] and lymphocyte function associated antigen 3 [CD58]. In our patient, we had detected absent and deficient levels of CD14, CD 55 and CD59.

Treatment of PNH has been largely empirical. Hemolysis is treated with blood transfusion if clinically required. Prednisone has a rapid beneficial in patients with hemolysis by diminishing complement activation [1]. Empiric use of steroids (Prednisone 20 to 40 mg/day) has resulted in controlling symptoms and stabilizing RBC values in a more than 50% of the patients [11]. Thrombosis is managed similar to other venous thrombosis occurring in other setting [1]. Thrombotic events are treated with anticoagulants for an indefinite time. PNH is not a malignant condition and spontaneous remission occurs in about 15% of patients, the role of stem cell transplantation is controversial and high-dose conditioning regimen is associated with considerable morbidity and mortality and thus cannot be the treatment of choice for patients with PNH [3]. Only sporadic reports on allogeneic stem cell transplantation for PNH are available. Whether or not to undertake allogeneic SCT is an extremely difficult decision. The use of allogeneic SCT for PNH should be decided by weighing the prognosis with conservative therapy against the risk of transplant-related mortality [3]. Bone marrow transplantation may be indicated in some patients, mainly those with severe life threatening disease or early in the course of the disease in children [1]. Eculizumab (Soliris) has been approved by healthcare authorities in the United States, European Union, Japan and other countries as the first treatment for patients with PNH. Soliris was approved in march 2007 by the U.S. Food and Drug Administration (FDA) as the first treatment for PNH. In June 2007 and January 2009, respectively, the European Commission (EC) and Health Canada also approved the use of soliris for the treatment of patients with PNH. Prior to these approvals, there was no therapy specifically available for the treatment of PNH. Eculizumab is a recombinant humanized monoclonal antibody directed against C5. Because C5 is common to all pathways of complement activation, blockade at this point aborts progression of the cascade regardless of the stimuli [12]. Blocking complement at this juncture prevents the genesis of the MAC complex and inhibits the release of the inflammatory mediator C5a. The mechanism of action of the drug eculizumab appears to prolong the survival of PNH Type III red cells in circulation and decrease the degree of hemolysis [9]. This drug shows a high affinity to C5 and when bound remains until the complex of drug-complement is removed from circulation [10]. Clinical trials with eculizumab show efficacy in lowering the incidence of intravascular hemolysis, lactate dehydrogenase (LDH), hemoglobinuria and transfusion requirements in patients with PNH. Eculizumab, a monoclonal antibody that blocks terminal complement activation, is highly effective in reducing hemolysis, improving quality of life, and reducing the risk for thrombosis in PNH patients. Eculizumab is recommended for patients with disabling fatigue, thromboses, transfusion dependence, frequent pain paroxysms, renal insufficiency, or other end-organ complications from disease [12].

Two weeks before starting therapy, all patients should be vaccinated against Neisseria meningitides because inhibition of complement at C5 increases the risk for developing infections with encapsulated organisms, particularly N. meningitides and N. gonorrhoeae [12]. Eculizumab is administered intravenously at a dose of 600 mg weekly for the first 4 weeks, then 900 mg biweekly starting on week 5. Eculizumab must be continued indefinitely because it does not treat the underlying cause of the disease. The patients should be monitored with a complete blood count, reticulocyte count, LDH and biochemical profile weekly for the first 4 weeks and then at least monthly thereafter [12]. The allogeneic bone marrow transplantation is recommended only for PNH patients with life-threatening cytopenias or patient with disabling hemolysis or thrombosis that is not controlled with eculizumab.

In conclusion all patients with Coombs test negative hemolytic anemia, refractory anemia and unexplained thrombosis in conjunction with cytopenias should be screened for paroxysmal nocturnal hemoglobinuria.

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RESUMEN

Hemoglobinuria paroxísmica nocturna es un desórden hematológico raro. Es una causa poco común de hemólisis intravascular, trombosis y supresión de la médula ósea. Presentamos un caso de una paciente femenina de 19 años quien fue admitida al hospital con un diagnóstico de pancitopenia. La paciente fue diagnosticada con PNH y respondió adecuadamente a transfusiones de sangre, esteroides y eculizumab. Discutimos la patofisiología, manisfestaciones clínicas y tratamiento de esta rara entidad.

COMPRESION TRONCO-ENCEFALICA PRECEDIDA POR NEURALGIA DEL TRIGEMINO EN UN PACIENTE CON DOLICOECTASIA VERTEBRO-BASILAR Y CAROTIDEA BILATERAL

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RESUMEN

Se describe un paciente que presentó neuralgia del trigémino izquierdo por dolicoectasia vertebro-basilar, a quien se le realizó una descompresión microvascular separando la arteria basilar del nervio trigémino interponiendo un fragmento de injerto vascular. Los síntomas resolvieron totalmente tras el procedimiento. Nueve años después, presenta recidiva del dolor facial asociado con síntomas compresivos de rápida progresión sobre el tronco encefálico. La resonancia magnética nuclear cerebral observó la dolicoectasia vertebro-basilar ejerciendo compresión sobre el aspecto ventro-lateral del puente y el bulbo raquídeo. En una angiografía cerebral se confirmó la presencia de dilatación tortuosa en las arterias vertebrales, basilares; así como de ambas carótidas internas. A nuestro conocimiento este es el primer caso de síndrome compresivo tronco-encefálico precedido por neuralgia del trigémino en pacientes con dolicoectasia vertebro-basilar y uno de los pocos casos de dolicoectasia vertebro-basilar y carotidea bilateral.

Palabras claves: *compresion, tronco-encefalica, neuralgia, trigemino, dolicoectasia, vertebro-basilar, carotida*

INTRODUCCION

La arteriopatía intracraneal dilatante (AID) describe una marcada elonganción, ensanchamiento y tortuosidad del sistema arterial, como consecuencia del adelgazamiento de la pared, degeneración de la lámina elástica interna, deficiencia en las fibras reticulares y atrofia del músculo liso; que afecta primordialmente las arterias vertebrales, basilar y carótida interna (ACI) distal (1, 2). En referencia a los vasos intracraneales, los términos AID y dolicoectasia (DE) son utilizados de forma indistinta (1). Otros sinónimos son megadolicoectasia, aneurismas fusiformes, aneurismas en forma de S, ectasia de la basilar y sistema arterial tortuoso (3).

El compromiso de la AID se manifiesta clínicamente por el desarrollo de eventos isquémicos a repetición en el territorio de la circulación anterior, mientras que en la afección vertebro-basilar puede producir disfunción cerebelosa, hidrocefalia, infartos cerebrales, déficit motores transitorios o persistentes, apnea del sueño, neuralgia del trigémino (NT), espasmo hemifacial, así como síndromes de compresión del tallo cerebral (4).

La NT es una de las manifestaciones más reconocidas de la DE del sistema vertebro-basilar, encontrándose en cerca del 1 - 2% de los casos (5), mientras que los reportes de casos de compresión del tronco-encefálico son escasos (6-8).

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Se describe el caso de un paciente quien debutó con una neuralgia del trigémino izquierdo, a quien se le realizó una descompresión microvascular con colocación de teflón, con mejoría sintomática tras el procedimiento. Nueve años después, presenta síntomas de compresión del puente y bulbo raquídeo.

Historia Clínica

Un paciente masculino, diestro, de 72 años de edad con antecedente de hipertensión arterial en tratamiento con metoprolol y losartán a quien se le realizó 9 años atrás una descompresión microvascular a través de una craniectomía retro-mastoidea por neuralgia severa de las ramas V2 y V3 del trigémino izquierdo interponiendo una pieza de de teflón. Tras el procedimiento el paciente presentó alivio total del dolor neuropático.

En los últimos 10 meses desarrolla recidiva el dolor neuropático en la división V2 izquierda, episodios intermitentes de vértigo, disminución de la agudeza auditiva del lado izquierdo; parestesias y debilidad del miembro superior izquierdo.

Al examen se encontró hipoestesia para dolor y temperatura en los dermatomas izquierdos de V1, V2 y V3; con alodinia en V2. Además, hipoacusia izquierda neurosensorial. Se demostró cuadriparesia espástica con fuerza muscular 3/5 en el lado izquierdo y 4/5 del lado derecho y pérdida de la sensibilidad para vibración, propiocepción y tacto ligero en hemicuerpo izquierdo. Los reflejos patelar, aquileo, estilo-radial, tricipital estaban exaltados del lado izquierdo. Los signos de Babinski, Gordon, Schaffer y Hoffman fueron positivos de forma bilateral.

Una resonancia magnética nuclear de cerebro simple y con gadolinio evidenció una dilatación de la arteria basilar y vertebral izquierda, comprimiendo el aspecto ventro-lateral del puente y bulbo raquídeo. La angiografía cerebral convencional demostró la dilatación tortuosa y uniforme de las arterias: vertebral izquierda (5 mm), vertebral derecha (4,8 mm), basilar (5, 7 mm), carótida interna izquierda (7,2 mm) y carótida interna derecha (7,4 mm) (ver Figura 1).

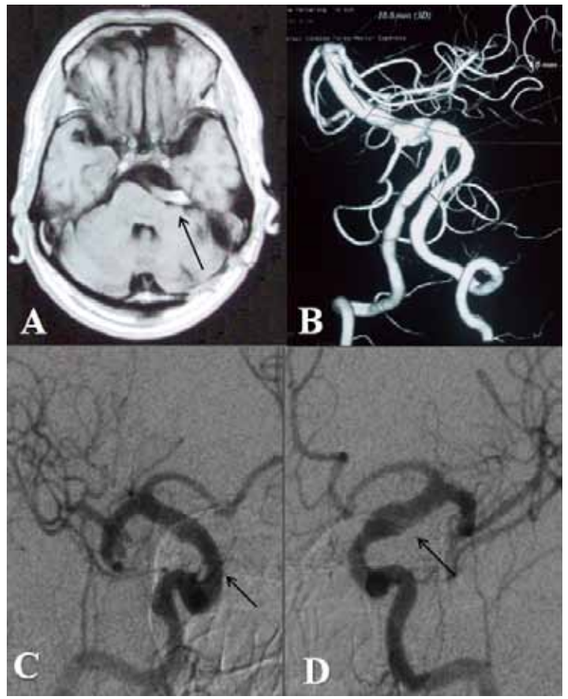

Figura 1. A: Resonancia magnética nuclear cerebral que demostró la dilatación tortuosa de la arteria basilar ejerciendo compresión sobre el aspecto ventro-lateral izquierdo de la protuberancia, en vecindad del recorrido del trigémino izquierdo (flecha). B: Angiografía cerebral convencional con reconstrucción 3-D: Se observó dilatación tortuosa de arteria vertebral y basilar (A). Proyección lateral de la arteria carótida interna derecha (C) e izquierda (D) con dolicoectasia bilateral nivel del segmento supra-clinoideo.

DISCUSION

La AID es una angiopatía de etiología aun no muy bien conocida. Se sospecha que se trata de una vasculopatía congénita de la pared elástica, que origina disfunción de la circulación posterior independiente del grado de aterosclerosis que afecte la íntima. Otros autores aseguran que se trata de una consecuencia de la hipertensión arterial prolongada sobre la lámina elástica interna y media de vasos anormales (6), lo cual concuerda con la aparición en pacientes jóvenes con síndrome de Marfan, enfermedad de Fabry, síndrome de Ehlers-Danlos, enfermedad Moyamoya, esclerosis tuberosa y síndrome de inmunodeficiencia adquirida (8).

La prevalencia de DE en la población general ha sido estimada en 0.05%–0.06%, sin embargo, es identificada en 12% de los pacientes con infartos cerebrales. La arteria basilar está afectada hasta en el 78% de los casos (2, 9), mientras que la afección de las carótidas es relativamente infrecuente (4). Asimismo, la DE simultánea de las arterias carótidas, vertebrales y basilar, como en el presente caso, es inusual y la literatura disponible deriva de reporte de casos aislados (10, 11).

El sistema vertebral-basilar debe considerarse elongado si la arteria basilar discurre lateralmente al margen del clivus o del dorsum sellae o si su bifurcación se encuentra por encima del plano de la cisterna supraselar. No existe un criterio cuantitativo preciso para arteriopatía dilatante, sin embargo, un mínimo de 4 mm de diámetro es requerido (5), aunque la mayoría de autores señalan 4,5 mm como punto de corte para considerar una dilatación ectásica (2). Por otro lado, Flemming y colaboradores propusieron un esquema de clasificación para los aneurismas vertebro-basilares no saculares en fusiformes, dolicoectásicos y transicionales; en la cual la DE se refiere a una dilatación uniforme de 1,5 veces el diámetro normal de la arteria y con algún grado de tortuosidad (12).

Para la definición de AID de la arteria carótida interna no ha sido establecido un diámetro mínimo de dilatación, sin embargo, el ensanchamiento por encima del los rangos normales (13) y la morfología arterial establecen el diagnóstico.

Las manifestaciones clínicas por DE pueden ser por compresión o fenómenos hemodinámicos. Levine y colaboradores (14) publicaron una revisión de la literatura en la que incluyó 128 pacientes con edad promedio de 59 +/- 11 años. Setenta y cuatro porciento eran hombres. Los principales síntomas fueron: eventos isquémicos de circulación posterior (48%), hidrocefalia (31%), hipertensión arterial (24%) y compresión de pares craneales (58%), especialmente el espasmo hemifacial (39%) y la NT (27%).

La presencia de un conflicto neural-vascular con la arteria basilar o vertebral causa el 1% y 2% de las NT, respectivamente, aún en pacientes sin DE. La DE vertebro-basilar es encontrada en cerca del 1% de los casos de NT (4, 5).

La compresión del tronco-cerebral por DE vertebro-basilar es menos frecuente. Kim y colaboradores en 1985 describieron el primer caso de compresión del bulbo raquídeo por esta causa (15). En 1995, Levine y colaboradores (14) encontraron 31 casos publicados de pacientes con síntomas de compresión del tallo cerebral. Por otra parte, una revisión de la literatura publicada en 2006 por Savitz y colaboradores describió tan solo 19 casos de compresión del bulbo raquídeo por DE de la arteria vertebral (8).

La cara antero-lateral del tallo cerebral es la más frecuentemente afectada, donde discurren los tractos cortico-espinales, espino-talámicos, espino-cerebelosos, el núcleo ambiguo; así como el origen aparente de los nervios craneales V, VII, VIII, IX, X y XII. Por esto, los hallazgos clínicos más frecuentes son motores, cerebelosos y vestibulares.

La extensión de la compresión no siempre se correlaciona con los hallazgos clínicos (8), lo cual sugiere que los cambios hemodinámicos pueden ser más elocuentes que el efecto de masa.

La DE es una enfermedad progresiva. Mangrum y colaboradores demostraron aumento del tamaño de los aneurismas vertebro-basilares no saculares en 48% de los casos seguidos por imagenología, en ocasiones acompañados de empeoramiento de la sintomatología. Existen casos en los que el rápido aumento del diámetro ha requerido procedimientos quirúrgicos de emergencias para descompresión del tronco cerebral (7).

El mejor tratamiento para la compresión tronco-encefálica por DE no ha sido establecido. La mayor parte de la literatura corresponde a reportes de casos aislados, tratados quirúrgicamente mediante descompresión microvascular, con lo que se usualmente se ha logrado mejoría sintomática.

En el presente caso, la manifestación inicial fue la neuralgia del trigémino, por lo que aun en presencia de la DE se indicó la descompresión microvascular mediante la colocación de teflón entre el nervio y la arteria. Debido a que la mayoría de los pacientes de los casos diagnosticadas por angiografía son asintomáticos (92.3% en la serie de Resta y colaboradores) (16) consideramos que en ese momento no estaba indicada ninguna técnica de reposicionamiento del sistema vertebro-basilar.

En los casos que se presentan con compresión del tallo cerebral algunos autores están en desacuerdo con la colocación de un material protésico en vecindad a la arteria dilatada, con la hipótesis que aumentaría los efectos compresivos. Por ello han sido descritas diferentes técnicas para descompresión, consistentes en la separación, movilización y fijación de la arteria lejos del tronco encefálico mediante la colocación de injertos vasculares e incluso con sutura de nylon (6).

Para el manejo de las DE de la carótida interna supra-clinoidea han sido utilizadas técnicas de ligadura proximal o trapping, con anastomosis de la arteria cerebral media con la temporal superficial, sin embargo, solo existen reportes de casos acerca de este tratamiento, por lo que su seguridad y efectividad requiere estudios adicionales (17).

La DE vertebro-basilar sintomática está asociada con alta morbilidad y mortalidad. En el estudio de Passero y colaboradores (18) fueron estudiados 156 pacientes durante un promedio de 11.7 años. Durante el seguimiento, 63% de los pacientes presentaron alguna complicación (infarto cerebral, hemorragia intra-craneal, hidrocefalia o síntomas compresivos), sin embargo, fueron más frecuentes en los pacientes con lesiones incidentales (29%) que en aquellos con síntomas compresivos (66%) o eventos cerebro-vasculares previos (70%). También se documentó progresión de la enfermedad en 43% de los pacientes, lo cual se encontró asociado con alta morbilidad y mortalidad. La proporción acumulada de sobrevivientes libres de efectos adversos fue 54.1 a 5 años, 39,5 a 10 años y 23,5% a 15 años. Este impacto sobre la salud justifica el desarrollo de estudios que permitan establecer una estrategia terapéutica efectiva y segura para el tratamiento de estos pacientes.

CONCLUSION

La AID es una enfermedad progresiva caracterizada por la elongación, ensanchamiento y tortuosidad del sistema arterial ocasionado por alteraciones de la pared vascular más prominentes en la circulación posterior, con manifestaciones variadas.

Su sintomatología deriva principalmente de sus efectos hemodinámicos y compresivos sobre los pares craneales y estructuras vecinas.

Se describió el caso de un paciente que presentó neuralgia del trigémino izquierdo por dolicoectasia vertebro-basilar, a quien se le realizó una descompresión microvascular con buena respuesta, sin embargo, nueve años después presentó síntomas rápidamente progresivos de compresión del tallo cerebral por las arterias vertebrales y basilar. En la angiografía cerebral también se encontró dolicoectasia de ambas carótidas internas.

Las manifestaciones clínicas de este paciente ilustran el carácter progresivo y difuso de la enfermedad, así como el espectro de manifestaciones clínicas que puede ocasionar.

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Reconocimientos

A Liceth Chadid del Servicio de Hemodinamia y a Carlos Valencia, del Servicio de Radiología de la Clínica Universitaria San Juan de Dios, por su colaboración en el procesamiento de las imágenes utilizadas en este escrito.

ABSTRACT

We described a patient who had left trigeminal neuralgia by vertebro-basilar dolichoectasia, who underwent microvascular decompression separating the basilar artery of the trigeminal nerve by interposing a vascular graft piece. Symptoms resolved completely after surgery. Nine years later, he has a recurrence of facial pain associated with rapidly progressive brainstem compressive symptoms. The brain MRI showed the vertebro-basilar dolichoectasia exerting compression on the ventral-lateral aspect of the pons and the medulla. In cerebral angiography confirmed the presence of dilated tortuous vertebral arteries, basilar, and of both internal carotid.

To our knowledge this is the first case of brain stem compression syndrome preceded by NT in patients with vertebro-basilar dolichoectasia and one of the few cases with coexistence of vertebro-basilar and bilateral carotid dolichoectasia.

PRIMARY ANGIOSARCOMA OF THE BREAST IN A PRE-MENOPAUSAL WOMEN

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ABSTRACT

This case report describes the clinical presentation, imaging findings and pathologic features of a rare aggressive breast tumor in a pre-menopausal woman, namely primary angiosarcoma. Recognition of this extremely rare entity is needed to make an early diagnosis, institute early therapy and eventually improve patient's survival.

Index Words: *primary, angiosarcoma, breast, pre-menopausal, women*

INTRODUCTION

Primary angiosarcoma of the breast is a rare and highly aggressive tumor [1]. It comprises 0.04% of all the breast tumors and approximately 8% of breast sarcomas [1]. It is most commonly seen in young patients (30-50 years) [1]. These tumors usually develop as a complication of a pre-existing conditions as prior breast radiation and chronic upper arm lymphedema associated to secondary angiosarcoma of the breast. The etiology of primary angiosarcoma remains unknown [1].

We present a case of a 32-year-old pre-menopausal woman with primary angiosarcoma of the breast seen at our oncology clinic. This case is being presented for its diagnostic difficulty and its rarity in the medical literature.

CASE HISTORY

A 32-year-old, married, G1, P2, A0, woman was evaluated at the oncology clinic with the chief complaint of left breast painless enlargement of five months duration. The patient had her menarche at 10 years of age. Past medical history was unremarkable for any systemic illness or toxic habits. There was no history of previous use of oral contraceptive pills. Patient received treatment for fertility three years ago. She had no family history of cancer. On physical examination, an induration was located in the left breast without any palpable mass, ulceration or necrotic changes in the overlying skin. The skin over the lesion was smooth and intact without evidence of lacerations, discoloration or hyperpigmentation. No axillary or supraclavicular lymph nodes were palpable. Patient denied tenderness, weight loss, nipple discharge or any constitutional symptoms.

The sonomammography in the superomedial aspect at 10 o'clock position in the left breast, showed an area of parenchymal distortion, coarsening and increased echogenicity probably inflammatory or infectious in origin. The mammography showed an area of increased density at the left breast superomedial aspect but no spiculated lesions or suspicious clusters of microcalcifications were seen. She underwent left breast core biopsy showing a vascular lesion of the breast with pleomorphism of endothelial cells and no mitosis, suspicious of angiosarcoma. This was followed by a left breast partial mastectomy revealing low grade angiosarcoma measuring 3.0 cm x 3.0 cm x 2.5 cm with negative margins [see Figures 1, 2 and 3]. However, a pathology review revealed high grade angiosarcoma, at least 3.0 cm in size and focally extending to within 1 mm of the black inked margin. The chest and abdomino/pelvic CT Scan were negatives for masses, enlarged nodes or visceromegaly. A bilateral breast MRI showed post-surgical changes of the left breast with post-surgical seroma measuring 2.6 cm x 4.7 cm and no suspicious enhancing lesions. There was no abnormal internal mammary chain or axillary lymphadenopathy by MRI. The PET/CT showed no evidence of residual or metastatic disease. A Bone Scan had mild degenerative inflammatory changes in the spine and sacroiliac joints. Patient underwent a left breast simple mastectomy showing benign breast tissue with biopsy site changes and no residual angiosarcoma. The sentinel node biopsy showed 0/3 nodules negative for malignancy. Patient was treated with chemotherapy (Taxol-Paclitaxel) 80 mg/m2 once a week for 12 weeks and received radiotherapy to the chest wall to decrease loco-regional recurrence of the disease. The patient completed the treatment successfully. Fifteen months after diagnosis, a re-evaluation with Chest CT Scan and breast MRI demostrated no evidence of recurrence of the disease. The patient remains well without

signs of recurrence of the disease 15 months after initial presentation and she is currently under follow up at the oncology clinic.

DISCUSSION

Angiosarcomas are rare malignant tumors that arise from endothelial cells lining vascular channels [3]. The breast is one of the most common sites in the body to develop an angiosarcoma [3]. There are no known risk factors for developing primary angiosarcoma [4]. Angiosarcoma of the breast can be divided into primary and secondary. Primary angiosarcomas of the breast occur sporadically in young women and usually present as palpable masses [3]. Secondary angiosarcomas occur most frequently after breast conservation therapy with radiation therapy; the average latency period is 5–6 years [3].

Histologically, angiosarcomas of the breast are classified into three grades: Grade 1 to Grade 3 or well to poorly differentiated [1]. It was believed that histologic grading of mammary angiosarcomas plays an important role in prognosis, but a recent study has shown that there is no correlation between histologic grade and patient outcome [1]. Low-grade tumors consist of anastomosing vascular channels that invade the surrounding breast tissue [3]. Intermediate-grade tumors have more solid neoplastic vascular growth and an increased mitotic rate [3]. High-grade lesions have frankly sarcomatous areas, as well as areas of necrosis, hemorrhage and infarction [3]. Multiple grades may exist in the same tumor, so grading from a core biopsy specimen may not be possible [3]. Complete excision and careful histologic evaluation are needed to accurately determine the tumor grade [3].

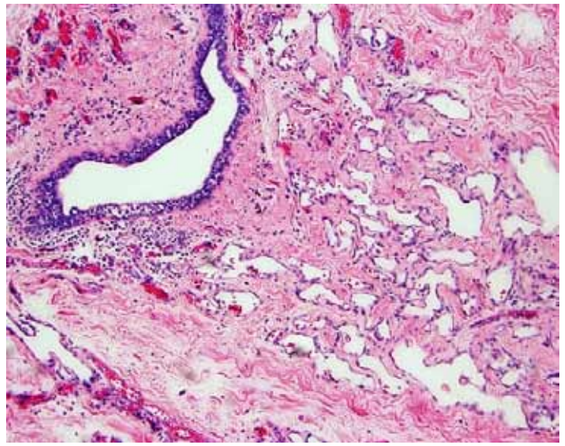
Patients with primary angiosarcoma present with a palpable mass that may be growing rapidly [3]. Bluish skin discoloration occurs in up to a third of patients and is thought to be attributable to the vascular nature of the tumor [3]. Secondary angiosarcomas usually are found in older women who have undergone breast cancer treatment [3]. The mean age at presentation is the late 60s [3]. There are two types of secondary angiosarcoma: lymphedema-associated cutaneous angiosarcoma and post-irradiation angiosarcoma [3]. Lymphedema-associated cutaneous angiosarcoma was first described in 1948 by Stewart and Treves; it develops on lymphedematous limbs and the chest wall after mastectomy and axillary lymph node dissection [3]. Increased use of breast conservation therapy and sentinel lymph node sampling has lowered the incidence of treatment-related lymphedema [3]. Post-irradiation angiosarcoma generally occurs after breast conservation therapy and radiation therapy and only rarely occurs after mastectomy [3]. It usually affects the dermis of the breast within the radiation field but may occasionally develop in the breast parenchyma [3]. The incidence of post-irradiation angiosarcoma appears to be low, ranging from 0.09–0.16% [3]. Patients with secondary angiosarcoma present with red plaques or nodules or with areas of skin discoloration, which may be mistaken for bruising and may delay the correct diagnosis [3]. Skin thickening due to angiosarcoma may be masked or misinterpreted as skin changes that occur after radiation therapy [3]. Sonographically, the dermal lesions may be difficult to differentiate from post-radiotherapy skin thickening [3].

The diagnosis of angiosarcoma can be extremely challenging. Mammogram may show a non-specific mass and up to one-third of the patients have no abnormalities [1]. Mammographically, the appearance is non-specific [3]. Mammograms may appear completely normal in 33% of cases of primary angiosarcoma, but this has also been reported in cases of secondary angiosarcoma [4]. Many women with primary breast angiosarcoma are young and the dense breast parenchyma that is characteristic of young women may obscure visualization of a mass [3]. MRI has become a useful tool for diagnosis [1]. MRI is useful in determining tumor extent and in planning surgery [3]. It also may detect residual disease after incisional biopsy [3].

Results from fine-needle aspiration and punch biopsies are generally not diagnostic [4]. The pre-operative difficulty in diagnosing these lesions may be attributable to a limitation in cells or tissue yielded by fine-needle aspiration cytology and tru-cut biopsy [6]. Fine needle aspiration has a low specificity with a false negative rate of 37% [1]. Findings from full-thickness incisional biopsies or excisional biopsy specimens should be conclusive, and these procedures are indicated if angiosarcoma is suspected [4]. PET with 18F-FDG may be used for staging of angiosarcoma [3].

The treatment is primarily surgical, either by mastectomy or wide excision [1]. There is no role of axillary dissection due to the low incidence of axillary metastasis [1]. The role of adjuvant therapy with radiotherapy and chemotherapy is equivocal. This is because of the small sample size in studies and the selection bias. Although there is no survival advantage, adjuvant radiotherapy has shown to reduce the local recurrence of the tumor [1]. It is reasonable to offer radiotherapy if there is a high risk of microscopic residual disease [1]. Metastatic tumors have shown response to combination cytotoxic chemotherapy (up to 48%) with anthracycline-ifosfamide or gemcitabine-taxane that suggests that angiosarcoma is likely to be a chemosensitive disease [1] [5]. Chemotherapy should be considered for patients with high-risk, localized breast angiosarcoma [1]. Almost all authors advocate aggressive surgical resection as the treatment of choice for angiosarcoma [4]. Although irradiation may seem to be a contradiction for a possibly radiation-induced tumor, surgery may be accompanied by hyperfractioned radiation therapy in patients with high-grade sarcoma in order to prevent recurrence [4]. The effect of systemic therapy (chemotherapy) has not yet been established [4].

Angiosarcoma carries a poor prognosis [1]. Five-year survival ranges from 8 to 50% [1]. Distant metastases have been seen in lung, skin, liver, bone, CNS, spleen, ovary and heart [1]. The nodal metastasis rate is low (6%) [1]. The prognostic factors for sarcoma of the breast include the tumor size, presence of residual disease and cellular pleomorphism [1]. According to a recent report, grade of the tumor may not be an important prognostic factor [1].



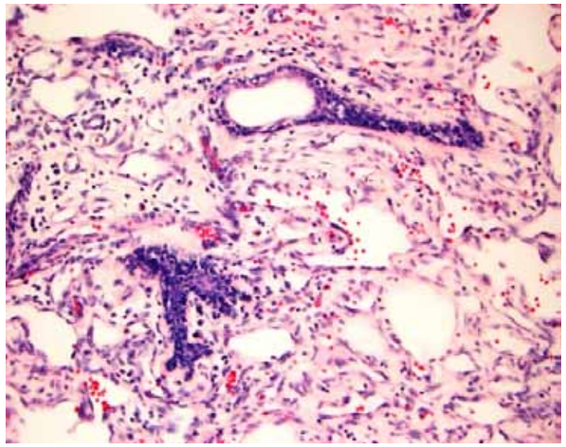


Figure 1: Angiosarcomas are malignant sarcomas of vascular endothelial cell origin.

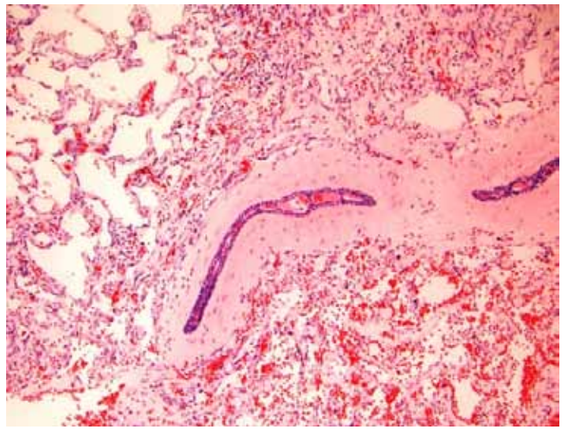


Figure 2: Angiosarcomas may be classified as grades I, II, or III. This correlates with well-differentiated, moderately differentiated and poorly differentiated tumors respectively. However, regardless of tumor grade, angiosarcomas tend to be aggressive.

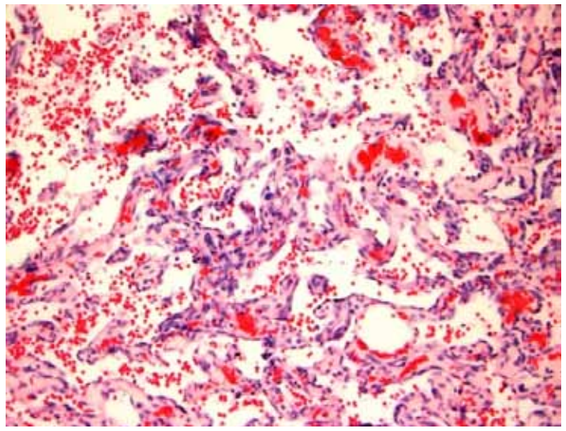


Figure 3: Angiosarcomas may form distinct blood vessel like (vascular) channels that are irregular in size and shape. Angiosarcomas may initially appear to be hemangiomas, a benign type of blood vessel tumor. However, a key difference is that the angiosarcoma vascular channels disrupt tissue planes and form a connecting network of sinusoids or pools.

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RESUMEN

Este reporte describe la presentación clínica, hallazgos de imagen y rasgos patológicos de un tumor raro de seno en una mujer pre-menopáusica. El reconocer esta rara entidad es importante para eventualmente hacer un diagnóstico y un tratamiento temprano y así combatir esta desafiante enfermedad mejorando la sobrevida de los pacientes.

PARAPHARYNGEAL SPACE TUMOR: UNDIFFERENTIATED SARCOMA OF THE PAROTID GLAND. A Case report

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ABSTRACT

Parapharyngeal space tumors are extremely uncommon. A 43-year-old man presents with a painless upper neck and face mass, airway obstruction and dysphagia. Physical evaluation revealed a firm, non-mobile mass extending from the right auricular region to the mandibular region of the neck. Radical parotidectomy was scheduled and muscle biopsy was done yielding undifferentiated sarcoma of the parotid gland. Parapharyngeal space tumors represent a problem for physicians in making an accurate diagnosis and determining management options available. Extensive knowledge of the anatomical boundaries of the parapharyngeal space, diversity of pathological problems and common clinical manifestations should help avoid delayed diagnosis and improve patient's outcome.

Index words*: parapharyngeal, space, tumor, sarcoma, parotid, gland*

INTRODUCTION

The parapharyngeal space is a potential space that is often described as having the shape of an inverted pyramid extending from the base of the skull to the greater cornu of the hyoid bone. Tumors of the parapharyngeal space are extremely uncommon, comprising only 0.5% of all head and neck tumors (1, 2). Tumors arising in this space may be of malignant or benign origin and represent a formidable diagnostic and therapeutic challenge due to the complex anatomy of this region. Since the majority of patients present with nonspecific symptoms and lesions become evident when sufficiently large as to produce a palpable lump in the head and neck region, they represent a problem to the assess of the condition. Thus complete knowledge of the structures found in this space along with the clinical manifestations and high degree of suspicion should help the physician to make an early diagnosis and identify patients who may benefit from surgical excision of the tumor. We report the clinical presentation, imaging studies, and surgical findings of a 43-year-old man with a parapharyngeal space tumor.

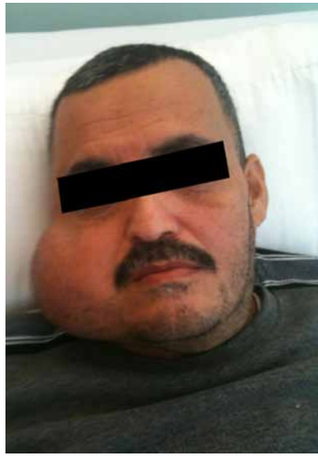
Case History

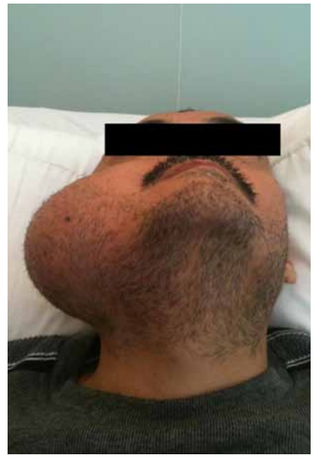
A 43-year-old man presented to our hospital referred by an otolaryngologist for evaluation of a painless upper neck and face mass on right side, airway obstruction and dysphagia. The patient first noticed a small bump approximately 1cm in the right cheek that slowly progressed in size fifteen months earlier associated with tinnitus in the right ear and occasional generalized headache. His past medical history was unremarkable except for depression and left preorbital trauma caused by a rock thrown at him. He was unemployed but used to work in construction and denied any kind of toxic habits. Family history was positive for Colon Cancer, Vulvar Cancer and Leukemia. Neck CT and MRI were performed initially at another institution. The MRI examination showed a large (7.5 x 7.0 x 6.0 cm) mass internal to the right mandibular ramus, mostly above the base of the tongue extending into the right lateral oropharynx; mild lateral displacement of the right parotid gland with a slightly enlarged submandibular gland; severe right mastoiditis. No major cervical lymphadenopathy was seen. The CT examination also revealed a large mass suggestive of soft tissue sarcoma situated mostly internal to the right mandible and ramus with lateral extension into the area of the medial aspects of the right parotid; mild to moderate compression of the lower nasopharyngeal airway. Fine needle aspiration of the right parotid gland was positive for spindle cell tumor consistent with a malignant neoplasm. He was evaluated by a Medical Oncologist and a Radio Oncologist, and was started on chemotherapy with 5-FU and Cisplatin. As referred by the patient, he only received six weekly sessions due to intolerance and poor compliance. He was initially evaluated by another ENT and was found not to be a surgical candidate. He then decided to look for a second opinion regarding management at another hospital. The case was reviewed at a Tumor Board meeting, reaching a diagnosis of pleomorphic adenoma of the parotid gland versus Sarcomatoid Tumor, and it was recommended to repeat the biopsy and to have a surgical opinion.

Thus, four months after the fine needle aspiration, an incision biopsy of the parotid gland was performed yielding hypercellular atypical stromal cells. Immediately after the last biopsy, the mass rapidly grew in size within a few months, leading to progressive difficulty breathing, dysphagia to solids, and weight loss of approximately fifty pounds, obstructive sleep apnea, and blurred vision. He decided to visit the CDT because of these symptoms, and was referred by the physician to an otolaryngologist. He was evaluated and referred to our hospital for evaluation and possible admission.

On physical evaluation the patient was alert and oriented in person, place and time. Vital signs: BP (120/68), P (110), R (19), T (36.6), weight (212), height (5'10"), BMI (30.4). Evaluation of the head and neck revealed a 17 x 12 x 12 cm firm, tender, non-mobile, non-pulsatile mass localized at the right side of the mid face (lateral aspect) extending from the auricular region to the mandibular region of the neck and pulling the lower eyelid, with involvement of the oral mucosa, found at the most posterior aspect of the gingivo-buccal sulcus and with extension to the right lateral oropharyngeal wall medially displacing the right tonsil and upper palate. The nasopharynx was found to be occupied by the well-encapsulated mass. The right nostril presented with 100% obstruction and the left nostril with 95% obstruction. There was also evidence of right ear canal erythema with accumulation of serum. Cranial nerves V, VII, VIII, IX, X, XI, XII, were intact. No evidence of trismus was found, but the patient had dysarthria. Pupils were reactive to light but there was evidence of anisocoria (left pupil was larger than the right). Extraocular movements were intact in the left eye but in the right eye the lateral rectus muscle was paralyzed. The trachea was slightly deviated to the left side. No lymphadenopathy was palpated. The chest appeared symmetrical with normal A/P diameter. Lungs were essentially clear to auscultation without wheezes or ronchi. On auscultation of the heart, it was found with a regular rate and rhythm, normal S1-S2, no murmurs or gallops present. The abdomen was soft, non-distended, without tenderness, rebound or guarding, and bowel sounds were normal, without palpable masses or visceromegaly. The extremities showed no edema or cyanosis; the peripheral pulses were normal. Neurologic examination no motor deficit was found except for neurologic dysfunction of the right abducens nerve; deep tendon reflexes were normal and sensation was intact (see Figure 1).

Investigations at Admission reported the following data: Laboratory: the hematocrit was 38.3 percent; the hemoglobin 13.1 g/dL; the white-cell count 9.0 K/uL, with 71 percent neutrophils, 20 percent lymphocytes, 9 percent monocytes, 0 percent eosinophils, and 0 percent basophils; the platelet count was 230 K/uL. Coagulation profile, basic metabolic panel, and urinalysis were essentially normal. EKG showed a normal sinus rhythm with normal axis and no acute ischemic changes (see Figure 2).





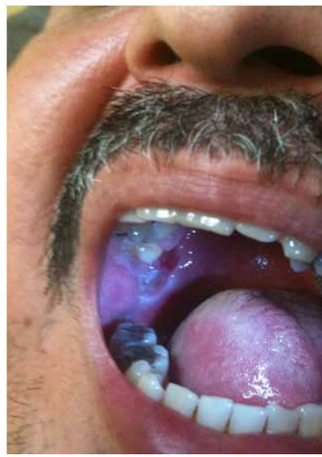


Figure 1: Parapharyngeal space tumor localized in upper mid face, extending to mandibular neck region with oropharyngeal involvement.

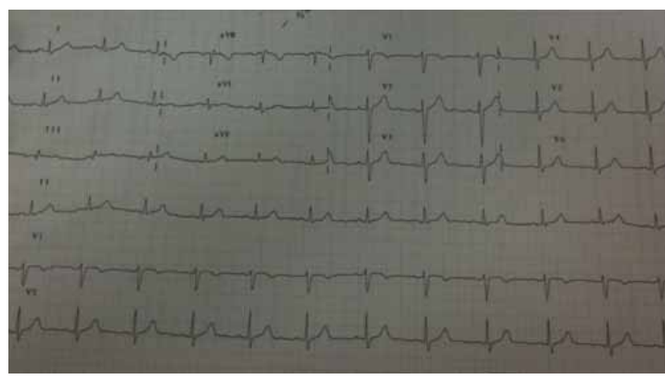


Figure 2: EKG

Chest X-ray revealed no acute cardiopulmonary pathology. Contrast CT of neck demonstrated an enhancing lesion involving most of the right aspect of the face and neck, displacing the proximal airway toward the left of the midline. Magnetic resonance imaging of the neck again disclosed a well encapsulated, homogeneous, large soft tissue mass, with central area of necrosis in the right side of the face, with involvement of the parotid gland, destruction of the right mandible, lateral wall of the maxillary sinus, and extending into the masticator muscles, oropharynx, and nasopharynx, with complete occlusion of the oropharyngeal and nasopharyngeal airway. There was also medial displacement of the carotid artery and jugular vein. Extensive bilateral cervical lymphadenopathy was also identified. Evaluation of the supratentorial portion of the brain showed no intra or extra-axial masses or lesions (see Figure 3).

The patient was admitted with the diagnosis of airway insufficiency, severe dysphagia and right parapharyngeal space tumor. ENT, Chemotherapyst, Radiotherapyst and Gastroenterologyst were consulted. He was evaluated by an otolaryngologist and a gastroenterologist and underwent tracheotomy and percutaneous endoscopic gastrostomy to relieve airway obstruction and dysphagia. The patient tolerated well both procedures, and was discharged home to be followed by the oncologic surgeon at another institution. He eventually was scheduled for radical parotidectomy. A cervical-parotid approach was performed with an incision extending superiorly in front of the ear to the neck area. Initial attempt at removal of the tumor resulted in sacrificing the facial nerve. During surgery, the mass appeared to be arising and was tightly attached to facial muscle tissue, laterally displacing the parotid gland, with involvement and destruction of the mandible (see Figure 4). Unfortunately the lesion was unresectable. Parotid gland and muscle biopsies were, done, showing undifferentiated sarcoma of the parotid gland. The patient currently has not received treatment but instead plans to travel to the mainland for further evaluation.

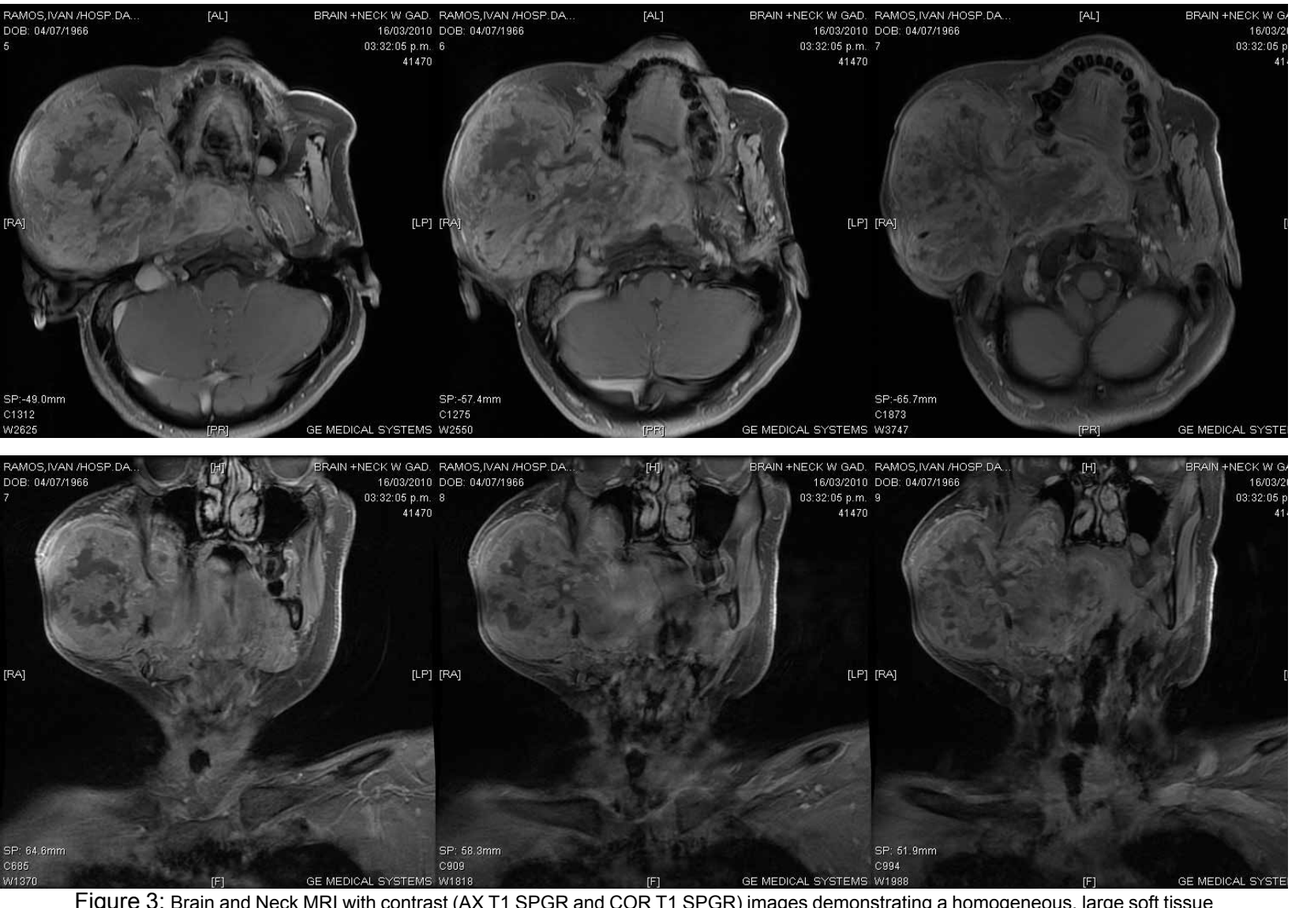


Figure 3: Brain and Neck MRI with contrast (AX T1 SPGR and COR T1 SPGR) images demonstrating a homogeneous, large soft tissue mass, localized in the right parapharyngeal space with involvement of the parotid gland, destruction of the right mandible, lateral wall of the maxillary sinus, with complete occlusion of the oropharyngeal and nasopharyngeal airway.

DISCUSSION

Tumors of the parapharyngeal space are uncommon, of these 70-80% are benign, and 20-30% are malignant (3). The majority of parapharyngeal space tumors encountered are salivary gland neoplasms (40-50%),

Fig. 4: Surgical incision extending superiorly in front of the right ear to the neck area, for identification of facial nerve.

located in the prestyloid compartment and may arise either from the deep lobe of the parotid gland or minor salivary glands. The most common benign prestyloid neoplasm is pleomorphic adenoma, 80-90% of salivary gland origin (3).

Malignant tumors of the salivary glands constitute approximately 1-3% of all head and neck malignancies and only 0.3% of all malignant neoplasms (6). Malignant neoplasms of the parotid gland are rare (20%), mucoepidermoid carcinoma is most frequently encountered, but others include adenoid cystic carcinomas, adenocarcinomas, and acinic cell carcinomas. Sarcomas account for 0.3% to 1.5% of all major salivary gland neoplasms (8, 9, 10). Of these, rhabdomyosarcoma and malignant fibrous histiocytoma (MFH) are the most frequently seen but others such as leiomyosarcoma, neurosarcoma, angiosarcoma, osteosarcoma, fibrosarcoma, liposarcoma, hemangiopericytoma, Kaposi's sarcoma, synovial sarcoma, and alveolar soft-part sarcoma can also be encountered (8, 9).

Other tumors commonly found in the parapharyngeal space are neurogenic lesions, (20-30%), schwannoma being the most commonly, found in the poststyloid space; approximately 20% are miscellaneous tumors or metastatic lesions.

The diagnosis of parapharyngeal space tumors is sometimes made incidentally during routine head and neck examination since most of them present as an asymptomatic neck or oropharyngeal mass. Tumors must at least reach a size of 2.0 cm to be palpable (3). Some of the manifestations of parapharyngeal space tumors are the following: hearing loss, pain (either stabbing character or occurring as a chronic sore throat), dysphagia, dyspnea, obstructive sleep apnea syndrome, cranial nerve deficits, Horner syndrome (ptosis, miosis, and anhydrosis), hoarseness, dysarthria and trismus.

Surgery is the mainstay of treatment for patients presenting with parapharyngeal space tumors. It is important to determine the size of the tumor and anatomical boundaries surrounding the lesion in order to consider the surgical approach. Nonoperative management should be considered in patients who have unresectable lesions; those who are poor surgical candidates; the elderly; those who fail balloon occlusion; and patients with slow growing, benign tumors who are at risk of damage to multiple cranial nerves due to resection of the lesion (3).

In this case the differential diagnosis included pleomorphic adenoma of the parotid gland or other benign tumors of salivary gland origin, but also malignant tumors such as sarcoma or metastatic lesions. In this patient, although the initial presentation and symptoms correlated with a benign tumor, surgical findings suggested a malignant neoplasm. Benign lesions are usually slow growing and painless. On the contrary pain, neurologic dysfunction (such as facial or vagus nerve palsy) and trismus are usually indicative of malignancy, although the majority of patients present with a painless, asymptomatic mass. Patients with malignant parotid tumors, 7-20% present with facial nerve weakness or paralysis, which almost never accompany benign lesions and indicate a poor prognosis (9). In our patient, neurologic dysfunction (such as facial or vagus nerve) was not evident except for motor nerve palsy of CN VI (abducens) possibly secondary to direct compression of the lateral rectus muscle by the tumor or through cavernous sinus infiltration. As evidenced on surgery and on pathologic findings, the lesion was a primary sarcoma of the parotid gland with metastasis to the mandible; the neoplasm did not appear to be an extension from adjacent muscle or bone. Undifferentiated sarcomas of the parotid gland (such as found in this patient) are uncommon, but a few cases have been previously reported in the literature. Although the mainstay of treatment is complete surgical excision, unresectable lesions, as in this patient, are usually managed with observation and radiation therapy.

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RESUMEN

Los tumores del espacio parafaríngeo son extremadamente poco comunes. Un masculino de 43 años de edad se presenta con una masa no dolorosa en la cara y el cuello, asociado a obstrucción de la vía aérea y disfagia. En la evaluación física, se observo una masa firme, no movible, extendiéndose desde la región auricular derecha hasta la región mandibular del cuello. El paciente fue sometido a una parotidectomia radical con biopsia, revelando un sarcoma no-diferenciado de la glándula parótida. Los tumores del espacio parafaríngeo representan un problema para los galenos en poder realizar un diagnóstico preciso y en determinar las opciones de manejos disponibles. Un conocimiento extenso acerca de la anatomía de este espacio, diversidad de problemas patológicos y manifestaciones clínicas comunes puede ayudar a evitar diagnósticos tardíos, y mejorar el pronóstico del paciente.

ABSTRACT

Within this review the author presents what kidney transplantation can and cannot do; it's state of the art; experience in Puerto Rico; major problems, obstacles and pitfalls; and the cutting edge of clinical transplantation and of transplantation immunology.

Index words: *kidney, transplantation, end stage renal disease.*

KIDNEY TRANSPLANTATION AS TREATMENT FOR END STAGE RENAL DISEASE

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INTRODUCTION

The transplantation field has evolved from initial pioneering scientific experiments into an accepted and the best current management of end stage organ failure. It has grown into a complex regulated field with important vectors and interactions with society, the government, industries, health care and insurance providers. However, the basis is and it continues to be scientific. Successful transplantations opened the doors to acceptance of more complicated elderly patients with a number of other co-morbidities, which have added complexity in the diagnosis and care of these patients. However, results hover in an excellent plateau, and quality of life and rehabilitation have improved beyond other organ replacement therapies. Challenges relate to immunological management, provision of healthcare and long term follow up, and cost issues. Active research in the quest for tolerance continues to advance and improve although with no spectacular breakthroughs. Nonetheless, with these Improvements, transplantation issues may be eventually solved. Donation, meanwhile, will always be a testimony of human goodness.

Clinical Considerations

End Stage Renal Disease (ESRD) is a major problem, especially in industrialized countries. It ranges from less than 40 pmp (per million population) in Bangladesh to 400 – 500 pmp in Mexico. Puerto Rico is close to 350 pmp. Prevalence follows the same pattern and it has been associated with indexes of development. The incidence has changed through the years from mostly glomerulonephritis and pyelonephritis to diabetes and hypertension.

Puerto Rico has one of the highest incidences of diabetes in the world, and diabetes is the most frequent cause of ESRD, 68%, the highest in the reported world (60 in Morelos, Mexico).

Thus, increasing age, diabetes, atherosclerosis, complications of hypertension, all added, have resulted in additional complexities in the management of these patients. The evaluation/selection process has to be much more detailed, and specialists in cardiology, urology, pneumology, vascular surgery and endocrinology must be included in the evaluation loop. With adequate treatment, many patients with cardiac or peripherovascular complications may be considered for transplantation.

Absolute contraindications for transplantation continue to be generalized cancer, generalized infection, untreatable cardiac or cerebrovascular disease, untreatable liver disease (unless considered for combined liver-kidney transplant), untreatable cardiac disease (unless considered for combined heart-kidney transplant), untreatable lung disease, unstable psychiatric disease, drug abuse, ABO incompatibility and sensitization against the intended donor. Of special concern are patients with obesity, non-compliant behavior in dialysis, smokers, lack of social or family support, hepatitis, the elderly, second or third transplants, and high level of sensitization.

Still, age-by-age, disease condition by disease condition, kidney transplantation confers a survival advantage over other forms of renal replacement therapy, with concurrent improvement in quality of life indexes and rehabilitation. However, in order to provide consistently superior results, transplantation should be carried out only in large hospitals, which have a full complement of all specialties and sub specialties, all tertiary support services, and around the clock availability.

On the downside, transplantation is not a panacea; it is not the cure for ESRD or any end stage organ failure. It requires the use of immunosuppressive medications

for the rest of the patient's life as well as monitoring of chemistries and general health by transplant specialists forever. Immunosuppressors have the general effect of decreasing the immune response and require careful monitoring and a system to provide immediate reaction to infections and tumors. Likewise, immunosupressors have an important effect on synthesis of DNA, RNA, proteins, and an important effect on the cell cycle, causing additional side effects, which must be identified and corrected. Some medications have organ or tissue specific effects that may require modification or substitution of some of the medications.

Fortunately, as in the current approach to chemotherapy of tumors, instead of one or two medications in high doses, the modern approach to immunosuppress patients is to use several medications in lower doses, and reliance on initial induction therapy, which although is not universally used yet, the tendency is for their increased use. We have been using induction since the early 1970's as will be described below.

Worldwide Experience

The concept of organ substitution has been in the collective mind of humanity for almost 5 millennia, having been suggested in the early book of medicine of the Yellow Emperor, 4.500 years ago. Other mythical and real substitutions have appeared sporadically through the last two millennia. However, success occurred after the pioneering work that culminated in the initial successful transplant of identical twins carried out in 1954 by Joseph Murray that won him the Nobel Prize. Others involved in leading the field were Moore, Lawler, Hume, Kuss, Hamberger, and more. Likewise, the advances in immunosuppression which made possible non-identical transplants, were pioneered by Calne, Monaco, Starzl, Zukosky, Najarian and more recently Cosimi and others. Clinical transplantation and immunosuppression have developed hand in hand with advances in basic immunology.

To date, around 1 million transplants have been carried out worldwide with results depending on the era, the region, and other factors including economy, availability of immunossupressors, training, etc.

In Latin America, the Latin American Transplant Registry, which was developed by us in Puerto Rico and by investigators in Brazil, reports close to 200,000 transplants in the region, with 130,000 kidney transplants. Brazil, because of its size leads the statistics followed by Mexico, Argentina, Chile and the larger countries. However, on a per million population basis, Puerto Rico and Uruguay lead the statistics of cadaveric donation and transplantation.

Experience in Puerto Rico

The early experience of peritoneal dialysis in Puerto Rico in the 1950's followed by the development of acute and chronic hemodialysis in the 1960's, led to renal transplantation. The first kidney transplants were performed in Ponce by the team of Drs. López Lotti, Alsina, Gutiérrez, Rodríguez Estapé and others. These initial pioneering efforts facilitated the development of formal structured programs by our group in the next decade.

Although a fully trained transplant-immunologist surgeon was onsite by late 1972, "transplantation awareness" at the time was low, resources were meager and there was no transplant hospital, organ procurement system or tissue typing laboratory. There was only a pioneer transplant law, "Ley de Donaciones Anatómicas" which allowed and promoted organ transplantation. However, a brain death law would have to wait for the next ten years. Similarly, there were immunology lectures, but there were no structured courses in basic and clinical immunology. These would be developed in the 1970's.

The first 135 transplants were carried out at the Veteran's Administration Hospital between 1977 and 1985. By 1980 it became clear that the patient population was mostly non-veteran, and arrangements were made by Government, University and Veteran's Administration officers to transfer activities to Auxilio Mutuo Hospital. In September 21, 1983 the first kidney transplant was carried out at Auxilio Mutuo Hospital, which has hosted the next 1500 plus transplants for a total of 1676. The first kidney-pancreas transplant was carried out in 2007 and now we have a total of 25 combined kidney-pancreas transplants. Table I summarizes the experience through the years. It can be seen from this table that the proportion of cadaver transplants increased markedly after the establishment of LifeLink of Puerto Rico in the mid-1990's.

The Transplant Program both at the VA and Auxilio Mutuo Hospitals has always had state of the art surgical techniques, tissue typing and immunosuppression. Indeed, the program has made contributions to the field through the years. Transplantations have been carried out on patients as young as a 3-year old weighing 10 kg, and to an 85-year old lady, who is currently an active 89, with excellent kidney function. We have performed close to 70 children and adolescents, 26 persons over 70 years and 4 persons over 80 years old, with good survival and function.

Protocols

Immunosuppression has always included polyclonal antibody induction, first, with Minnesota ALG and currently with Thymoglobulin. These probably have had a major effect in our long term results. Recently, we have also used monoclonals in low risk live donor transplants. The chronic schedule consists in calcineuric inhibitors, more recently tacrolimus, as well as antimetabolytes, more recently mycophenolates and derivatives. mTOR blockers have also been used. The protocols, of course, have evolved with new advancements as they evolve worldwide.

Results

Since its inception, and probably because of the immunosuppressive regime, the management of the patients in the context of a program, and a careful follow up, our results has always been average or higher than national average. Our current results are shown on Table II. In recent years they have been one or two points above national average.

Organ Donation was meager in the first 20 years of our existence. Although the team was quite aware of what it took to develop an organ procurement organization (OPO), it was impossible to obtain government or institutional funding to develop an OPO. However, we invited LifeLink to come to Puerto Rico and after a hesitant start in 1995 to 1998, and mostly because of organizational and protocol changes, organ donation improved steadily and markedly, and in recent years, we have had one of the best donation rates in Latin America, higher than the national average in the USA, and in one specific year, 2007, second only to Spain which has the highest donation rate in the world. This achievement had the important downstream effect of increasing cadaver organ transplantation and overall transplantation rates as well.

Contributions from Puerto Rico

Puerto Rico has spearheaded a number of important international initiatives, including the co-foundation of the Pan American Society for Dialysis and Transplantation, the Society of Transplantation of Latin America and the Caribbean, and the Latin American Transplant Registry. Similarly, our faculty has held national and international office in The Transplantation Society, American Society of Transplant Surgeons, United Network for Organ Sharing, the former International Society for Organ Sharing (now the International Society for Organ Donation and Transplantation), the Southeastern Organ Procurement Foundation, and several Latin America nutrition and immunology societies. We have published close to 200 scientific papers and more than 130 abstracts, more than 120 essays and special articles, and the faculty are frequent guest speakers in local and international forums. The author edited the only transplant books in Spanish and Octavio Ruiz Speare from Mexico, with two sold-out editions, one in 1988 and one in 2000. Other textbooks are being prepared. Participation of this faculty has been important in assisting other centers in Latin America and the Caribbean in their development. Transplant surgical, immunological, and nephrology fellows have been trained from Puerto Rico, El Salvador, Costa Rica, Mexico, Dominican Republic, Cuba, Venezuela, Bolivia, and other countries. Local nephrology fellows from the Veterans Administration Hospital and University of Puerto Rico, as well as surgical, medical, immunology and infectious disease fellows and medical students rotate through the program. The interns for the Master Degree Program from the School of Rehabilitation Counseling are also routine rotations in the program. We have had close to 100 research and transplant fellows and students, and over 600 clinical and resident and students rotations.

Problems and obstacles

Transplant centers in the US and in Puerto Rico currently struggle with conflicting directives from within and from government mandates. On one hand, the pressure of growing waiting lists for organ transplants (Puerto Rico over 400; nationwide, 100,000) has imposed the use of extended criteria donors, extended criteria kidneys and donations after cardiac death organs. Almost by definition these entail potentially decreased function. At the same time, the clinical results of patient and graft survival are continuously monitored both by the government and the United Network for Organ Sharing, and excellent performance is required. Finally, reimbursements by federal agencies and health insurances have failed to increase and in many cases have decreased, with an important impact on hospital as well as physician services. These three conflicting mandates require highly specialized clinical, administrative and financial teams to fine-tune the services in order to achieve optimal balance. However, quantity, quality and low reimbursements may collide in the future.

Part of the cost containment efforts by many insurance companies as well as Medicare has targeted immunosuppression, forcing the use of generic immunosuppressants to patients. Although generics are an excellent way to achieve cost containment in other areas and with other medications, drugs that require monitoring of doses and which have narrow therapeutic windows, such as neurologic and anticonvulsant drugs and immunosuppresants, are affected by this. Even though the majority of patients do well with close follow up, there are a number of patients where normal function decreased to the point of losing the organ. The efforts in monitoring these patients, in writing to the insurance companies, in additional hospitalization for management, in the organs lost, should be a factor to be considered by policy makers.

Non-compliance by definition carries with it an element of failed responsibility towards one self and towards society regardless of its cause. However, our experience with an increased number of non compliant patients, has identified a number of other factors including; (1) false security ("I'm doing well, I'm strong, I'm working, I feel healthy"), (2) misguided priorities ("I was the caregiver at home, I have a lot of work, I have many examinations to take at my school"…), (3) financial issues ("I have no money to pay the toll, to pay transportation for the clinic visits, to pay medications, to give the co-pay for medications"), (4) follow up by persons who have limited knowledge of immunology or immunosuppression, and are unaware of the urgency which is needed to deal with complications or minor changes in the laboratories (no reaction to new onset low grade proteinuria, minor changes in creatinine, minor changes in levels, apparently minor infections, apparently minor skin tumors). These issues have been identified using the fishbone techniques of quality programs, but now must be addressed in depth and in an organized approach.

The impact of increased organ donation resulting in increased transplantation has imposed additional demands on the institutional infrastructure of centers, especially in space and in systems. Although, this has been attended to, the continuing growth of transplantation

will require novel approaches to solve the issue of long term post transplant care.

Side effects of immunosuppressors, although decreased from what they used to be in the prednisone/azathioprine era, are still prevalent and must be addressed by the centers. These include organ specific effects, most notable in the bone marrow and the gastrointestinal tract. Infections and tumors require early and aggressive treatment in the presence of immunosuppression, much more than in normal persons. Among these factors, a notable increase in polyoma (BKV) virus has been observed in US and in Puerto Rico and is being actively studied. From our studies and the national experience, a decrease in immunosuppression with continuous monitoring has helped control this complication.

Success in the early management of rejection has resulted in a much-improved patient and graft survival. However, long-term immunological and non-immunological complications have emerged, leading to long-term organ loss. This loss has been adscribed to chronic immunosuppression, chronic allograft nephropathy (a term no longer used) and chronic rejection. The latter seems to be the most important cause since it has been shown by many (we are currently studying this issue in our lab). Point single antibodies develop against HLA antigens both specific and non-specific. Similarly, the infirmities which occur with age and some immunossupressors, such as those related to heart and vascular disease have continued to appear unquenched as they would have with other forms of renal replacement therapy. A lot of effort has been directed to these areas since prevention and early management are important therapeutic goals.

Paucity of organ donors is also limiting the management of these patients. Other approaches such as the ones described above, have increased the numbers, but not significantly curtailed the growth of the list. This has unfortunately brought the issue of transplant tourism which has made its growth in the Middle East and Asia and some places in Latin America. The results of these transplants are not optimal because of the selection of donors and the transmission of diseases. Also, from the ethical point of view, the enticement of economically disadvantaged populations is unacceptable.

The future

Current efforts continue to be directed towards that elusive holy grail of transplantation tolerance. Several centers in Europe and the US pursue this actively in a number of novel ways, including microencapsulated cells (we performed initial experiments in the 1970's in our lab), prevention of transplant-induced ischemia reperfusion injury, and its effect downstream in increased antigenecity and organ recognition; induction of donor specific tolerance using a variety of antibodies against receptors and accessory molecules, and promoting regulatory (suppressor) T-cell expansion stem cell transplantation; intracellular blockage of specific and non specific intracellular transport molecules; dendritic cell expansion; blockage of toll-like receptors and other surface receptors; new immunosuppresors; bioinformatic databases; urinary cell profiling; ongoing experiments on the xeno transplantation of cells and organs; and experiments in organ scaffolds with cell repopulation.

Parallel developments in immunological knowledge and techniques which may have direct or indirect applications in the prevention of rejection and development of tolerance include various approaches towards the development of artificial protein and lipid containers to deliver medications; the use of siRNA to affect and modulate RNA intracellularly; the identification of different gene patterns; gene regulation by interfering of RNA post transcriptionally; genetic testing; advances in angiogenesis; advances in apoptopic cell recognition and clearance; adhesion science; biomaterial or tissue engineering; metaloproteinases; nanotechnology as applied to biological antisera (nanobodies); and epigenetic interventions (controlled, directed methylations). This marvelous field of epigenetics has possible application with epigenetic reprogramming and specific cell development. Epigenetics may well be one efferent limb of systems biology.

RESUMEN

En esta reseña el autor presenta lo que trasplante de riñón puede y no puede lograr, su estado actualizado; la experiencia en Puerto Rico, los problemas mayores, obstáculos y escollos, a lo largo de el elemento importante en el trasplante clínico y la inmunología de trasplante.

2010 SRTR stats (in%)

Deceased Donor Patient Survival 1yr 97.8, 3yr 96.1
Living Donor Patient Survival 1yr 100, 3yr 92.7

Deceased Donor Graft Survival 1yr 97.3, 3yr 89.6
Living Donor Graft Survival 1yr 100, 3yr 88.6

TRANSPLANT CENTER
JANUARY 1977 - MARCH 11, 2011

RENAL TRANSPLANT PROGRAM K/P PROGRAM

			LIVE RELATED		LIVE RELATED		TOTAL			
	CADAVER DONOR		DONORS		DONORS		RENAL	KIDNEY	PANCREAS	
YEAR	LOCAL	USA	1st DEGREE	2nd DEGREE	HUSBAND WIFE	OTHERS	TX'S	PANCREAS	ONLY	TOTAL
1977	3	0	21	0	0	0	24	0	0	24
1978	3	2	10	0	0	1	16	0	0	16
1979	0	3	6	1	0	1	11	0	0	11
1980	0	2	16	0	0	2	20	0	0	20
1981	0	1	15	0	0	0	16	0	0	16
1982	0	1	11	2	0	0	14	0	0	14
1983	0	0	21	0	0	0	21	0	0	21
1984	6	6	14	1	0	0	27	0	0	27
1985	6	15	23	0	0	0	44	0	0	44
1986	5	16	20	2	0	0	43	0	0	43
1987	13	7	9	2	0	0	31	0	0	31
1988	14	4	12	0	0	0	30	0	0	30
1989	11	0	23	0	0	0	34	0	0	34
1990	6	7	17	1	4	0	35	0	0	35
1991	3	6	17	3	4	3	36	0	0	36
1992	3	6	23	0	5	1	38	0	0	38
1993	11	2	16	4	1	3	37	0	0	37
1994	7	6	18	1	0	0	32	0	0	32
1995	6	6	19	0	5	1	37	0	0	37
1996	4	3	14	0	4	0	25	0	0	25
1997	10	5	18	2	6	0	41	0	0	41
1998	30	10	27	1	2	1	71	0	0	71
1999	27	5	17	2	3	2	56	0	0	56
2000	21	16	21	1	5	4	68	0	0	68
2001	42	17	18	3	7	4	91	0	0	91
2002	32	10	20	3	3	0	68	0	0	68
2003	44	12	16	4	3	5	84	0	0	84
2004	47	15	16	1	3	4	86	0	0	86
2005	78	9	14	1	5	2	109	0	0	109
2006	49	12	6	1	5	2	75	0	0	75
2007	75	11	7	0	2	0	95	5	0	100
2008	52	16	11	1	3	4	87	7	0	94
2009	58	11	10	0	0	1	80	6	0	86
2010	66	3	6	1	2	2	80	7	0	87
2011	10	1	1	0	0	0	12	1	1	14
TOTAL	**742**	**246**	**533**	**38**	**72**	**43**	**1674**	**26**	**1**	**1701**

* Included one auto-transplant each for 1978, 1979 and 2 for 1980
** Included one (1) Kidney/Heart Tx.

GENERAL CONCEPTS IN THE MANAGEMENT OF A KIDNEY TRANSPLANT

ABSTRACT

The management of a kidney transplant patient is, in most cases, challenging and requires a multidisciplinary approach. For the physician caring for the patient it is imperative to have a broad knowledge regarding several concepts on their management, as they are increasingly faced with long-term care. Baseline rapport and accessibility provides a pivotal role in the treatment, monitoring and preventive measures in the kidney transplant patient. Currently, most aspects regarding patient management vary according to each transplant center. This article describes the importance of several medical issues directed towards the clinician aiming to improve awareness and expand knowledge, with the development of a systematic approach.

Index words: *concepts, management, kidney trasplant*

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INTRODUCTION

The first living organ transplant was performed on identical twin brothers. Richard Herrick received one kidney from his twin brother Ronald two days before Christmas in 1954. Dr. Joseph Murray performed the surgery in Peter Bent Brigham Hospital, Boston and in 1990 earned the Nobel Prize for this landmark procedure. Since then, advances in transplant medicine have broadened our understanding about immunological, metabolic, cardiovascular, obstetrical, infectious, oncological aspects along with an increased complexity for its management. The pivotal role of the clinician in the management of kidney transplant patient is crucial and is in most cases a challenge. This article provides a general guideline about important aspects on the management of the renal transplant patient.

When to evaluate for rejection and how to manage?

Allograft rejection is most often related to noncompliance with medications, and early recognition along with adequate treatment is essential to prevent allograft loss. Elevation of serum creatinine of 15% from baseline defines graft dysfunction [1, 2]. There are several types of allograft rejection and differ both on the time frame after transplantation and pathophysiological aspects. In the first week post-transplant, graft dysfunction may be the result of acute tubular necrosis, hyperacute /accelerated rejection, urologic abnormalities (obstruction, urine leak), or vascular thrombosis (renal artery or vein).

Before week twelve after transplantation differential diagnosis on graft dysfunction includes acute rejection, calcineurin inhibitor toxicity, volume contraction, urologic obstruction, infection (pyelonephritis, viral), interstitial nephritis, recurrent disease.

After twelve-weeks post transplant one must evaluate for the possibilities of acute rejection, volume contraction, calcineurin inhibitor toxicity, urinary obstruction, infection (pyelonephritis, viral), chronic allograft nephropathy, recurrent disease, renal artery stenosis, and post transplant lymphoproliferative disorder. When rejection is suspected the clinician should perform a complete physical examination, evaluate current medications, and order laboratories to include immunosuppressive agents levels, urinalysis, complete blood count, basic metabolic panel and virologic analysis (CMV, EBV, BK virus), renal transplant ultrasound and duplex. Nevertheless, allograft biopsy remains the gold standard for confirming the diagnosis of acute rejection. The biopsy will provide important information regarding the cause, activity and degree of irreversible damage. An adequate biopsy should include at least ten glomeruli with two arteries and is classified according to Banff 2007 criteria (See Table 1).

For hyperacute rejection no therapy has been found to be effective, and in most cases immediate graft nephrectomy is indicated.

The choice of treatment for acute rejection depends on the histological severity and type of rejection process (Antibody vs. cellular). Treatment for antibody-mediated rejection involves the reduction/removal of circulating antidonor antibodies with plasmapheresis and intravenous immunoglobulin, also rabbit antithymocyte globulin (ATG) and/or high dose steroids. At this moment no controlled trials have examined the treatment of antibody mediated rejection. On the other hand treatment for acute cellular rejection includes corticosteroids, and antilymphocyte regimens (rabbit ATG, OKT3, alemtuzumab) [1].

Table 1. Banff 2007 Criteria for Allograft Pathology

1.Normal
2.Antibody mediated chances (may coincide with categories 3, 4, and 5)
C4d deposition without morphologic evidence of active rejection
C4d+, presence of circulating antidonor antibody, no signs of acute or chronic TCMR or ACMR
Acute antibody mediated rejection
C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury such as (Type/Grade):
I.ATN like minimal inflammation
II. Capillary and glomerular inflammation (ptc/g>0) and/or thromboses
III. Arterial –v3
Chronic active antibody mediated rejection
C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrosis.
3.Borderline Changes
Suspicious for acute T cell mediated rejection. No intimal arteritis, but foci of tubulitis (t1, t2, or t3) with minor interstitial inflammation (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis (t1, i1 or greater)
4.T cell mediated rejection (TCMR; may coincide with 2, 5, 6)
Acute T cell mediated rejection (Type/Grade)
IA. Significant interstitial infiltration (i2; >25% of parenchyma affected) and foci of moderate tubulitis (t2; >4 mononuclear cells/tubular cross section or group of 10 tubular cells)
IB. Significant interstitial infiltration (i2; >25% of parenchyma affected) and foci of severe tubulitis (t3; >10 mononuclear cells/tubular cross section or group of 10 tubular cells)
IIA. Mild to moderate intimal arteritis (v1)
IIB. Severe intimal arteritis comprising > 25% of the luminal area (v2)
III. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle
Chronic active T-cell mediated rejection
Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration)
5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology (Grade)
I. Mild interstitial fibrosis (ci1) and tubular atrophy (ct1) < 25% of cortical area affected
II. Moderate interstitial fibrosis (ci2) and tubular atrophy (ct2); 26-50% of cortical area affected
III. Severe interstitial fibrosis (ci3) and tubular atrophy (ct3) > 50% of cortical area affected
6. Other changes not considered to be due to rejection – acute and/or chronic (may coincide with categories 2, 3, 4, and 5)

What are the most important metabolic problems?

New-onset Diabetes Mellitus after transplantation occurs in up to 50% of cases. Risk factors include ethnicity (African American, Indo-Asian, Hispanic), obesity, older age, male gender, family history of Diabetes, personal history of Impaired Glucose Tolerance, viral infections (HCV, CMV), Hypertriglyceridemia, Hypertension, immunosuppressive therapy (corticosteroids, tacrolimus, and cyclosporine to a lesser extent)[3]. One postulated theory is that calcineurin inhibitor-based are toxic to pancreatic beta cells, therefore, reducing insulin secretion. Recent studies suggest that most importantly, there is reduced insulin sensitivity, which will in turn, play a role in the development of cardiovascular disease [4]. Management should follow the conventional approach for patients with type 2 Diabetes Mellitus (See Table 2).

Dyslipidemia is a common problem following transplantation that has been linked to the effects of immunosuppressive agents. Tacrolimus has been associated with better lipid profiles when compared with cyclosporine, which in turn has better profiles than sirolimus. All transplant patients should be treated as coronary artery disease risk equivalent with targets of total cholesterol less than 200 mg/dL and LDL level less than 100 mg/dL. One important aspect of treatment is that concomitant use of statins and calcineurin inhibitors, particularly cyclosporine, increases the risk of rhabdomyolysis [4].

What are the musculoskeletal aspects to consider?

Osteoporosis may occur in up to 60% of kidney transplant patient that can be attributed to the use of corticosteroids, calcineurin-inhibitors, the duration of chronic kidney disease and dialysis, persistent metabolic acidosis, persistent hyperparathyroidism, vitamin D deficiency or resistance, phosphate depletion, diabetes mellitus, hypogonadism, and smoking. Osteopenia is managed with vitamin D and calcium supplementation and progression to osteoporosis is an indication for biphosphonate therapy. Early steroid withdrawal during the first post transplantation year has been shown to reduce the incidence of osteoporosis [4].

Other important problem to consider is avascular necrosis. An incidence of 3 to 6% has been reported, mainly affecting the femoral head and neck.

Table 2. Management of New-onset Diabetes Mellitus after transplantation

Dietary Modification
Dietitian referral
For diabetic dyslipidemia: a diet low in saturated fats and cholesterol and high in complex carbohydrates and fiber is recommended
Lifestyle Modification
Exercise
Weight reduction or avoidance of excessive weight gain
Smoking cessation
Adjustment or Modification in Immunosuppressive Medications
Rapid steroid taper, steroid sparing or steroid avoidance protocols
Tacrolimus cyclosporine conversion therapy
Calcineurin inhibitor withdrawal
Pharmacologic Therapy
Acute, marked hyperglycemia (may require inpatient management)
Intensive insulin therapy (consider insulin infusion when glucose > 400 mg/dl
Chronic Hyperglycemia: Treat to Target Hemoglobin A1c < 6.5%
Oral glucose lowering agent monotherapy or combination therapy and/or insulin therapy
Consider Endocrinologist referral if hemoglobin A1c remains > 9.0%
Monitoring of patients with New-onset Diabetes Mellitus after transplantation
Hemoglobin A1c every 3 months
Screening microalbuminuria
Regular ophthalmologic examination
Regular foot care
Annual fasting lipid profile
Aggressive treatment of dyslipidemia and hypertension

Magnetic resonance imaging is the modality of choice for the diagnosis, and treatment includes femoral head decompression or total hip replacement.

Finally, hyperuricemia and gout are common in patients receiving cyclosporine-based immunosuppression, which is due to impaired uric acid renal excretion by inhibiting proximal tubular secretion. Management of acute gouty attacks is standard, however the use of anti-inflammatory agents should be avoided with a glomerular filtration rate less than 60ml/min. Long-term prophylaxis includes reduction or discontinuation of diuretics, allopurinol, dietary modifications, and switching cyclosporine to tacrolimus.

How to manage cardiovascular aspects?

Cardiovascular disease is the leading cause of death in transplanted patients. Cardiovascular risk increases up to 10-fold when compared with the general population and correlates with a serum creatinine level greater than 1.5 mg/dL [2]. Management recommendations include dietary modifications, discontinuing smoking, control of blood pressure, glucose and lipid levels. Blood pressure target should be a systolic pressure below 130 mm Hg and diastolic below 80 mm Hg. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the most widely used regimes due to their safety, efficacy and well-established renoprotective, antiproteinuric, and cardioprotective effects [4].

How about pregnancy and fertility?

Pregnancy has become common after transplantation. Menstruation and fertility resume in most women within the first year after transplantation. Over 90% of pregnancies that proceed beyond the first trimester succeed. The criteria for considering pregnancy in kidney transplant recipients are good health and stable kidney function for 1 to 2 years after transplantation with no recent acute or ongoing rejection or infections, absent or minimal proteinuria (less than 0.5 g/d), normal blood pressure or easily managed hypertension, no evidence of pelvicaliceal distension on ultrasonography before conception, serum creatinine concentration less than 1.5 mg/dL, and in terms of drug therapy, prednisone 15 mg/d or less, azathioprine 2 mg/kg or less, and cyclosporine less than 5 mg/kg/d. Among immunosuppressive agents, mycophenolate/mycophenolic acid (MMF) is category D and should be discontinued before pregnancy. The safest regimen during pregnancy seems to be a combination of calcineurin inhibitor and prednisone. In men, the use of sirolimus has been associated with significant reductions in sperm count and motility [5]. The use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in the pregnant patient.

What are some of the important infections to consider?

Kidney transplant patients are at increased risk for the development of infections and they follow a predictable timeline from the time of transplantation (See Table 3). Other important factor determining infections include level of immunosuppression, epidemiological factors including seropositivity status of donor and recipient, presence of graft versus host disease, and prophylaxis therapy provided [4].

Table 3. Infections following renal transplantation

Month 1 After transplantation
Postoperative bacterial infections : Urinary tract, Respiratory, Vascular access related wound
Nosocomial, including Legionella species
Viral: HSV
Fungal: Candida
Organisms transmitted with donor organ
Untreated infection in recipient
Months 1 – 6
Opportunistic or unconventional infections
-Viral : CMV, HH-6, HHV-7, EBV, VZV, influenza, RSV, adenovirus
Fungal : Aspergillus species, Cryptococcus, Mucor
Bacterial : Nocardia, Listeria
Mycobacterium species, Legionella, tuberculosis
Parasitic : Pnemocystis jirovecci
Toxoplasma and Strogyloides species, leishmaniasis
HBV,HCV,HIV
After 6 Months
Late opportunistic infections
-Cryptococus, CMV retinitis or colitis, VZV, parvovirus B-19, polyomavirus (BK,JC), Listeria, tuberculosis
Persistent infections ; HBV, HCV
Associated with malignancy : EBV, papillomavirus, HSV, HHV-8
Community acquired
Unusual sites : paravertebral abscess

Cytomegalovirus (CMV) represents a significant cause of morbidity during the first six months of transplantation. Presentation may be one of primary infection (donor seropositive, recipient seronegative), reactivation (recipient seropositive), or superinfection (both seropositive). Clinical manifestations range from a mononucleosis-like illness to tissue invading disease including hepatitis, esophagitis, gastroenteritis, colitis, pneumonia, and allograft dysfunction. Prophylactic therapy is particular of each transplant center, and pre-emptive therapy according to surveillance viremia is lately being adopted.

BK virus has increasingly been associated with allograft dysfunction and loss. Manifestations may include hematuria, pyuria, and ureteral stenosis. Detecting the virus in urine, blood and renal tissue makes diagnosis. The detection of decoy cells by urine cytology is a sensitive (100%) measure but has a low positive predictive value (29%) and represents a good screening test but is not diagnostic of BK virus nephritis. Renal biopsy is the gold standard for the diagnosis of BK virus. Mainstay of management remains immunosuppressive therapy adjustments and antiviral agents [7].

Is vaccination indicated?

All potential transplantation candidates should complete all recommended vaccinations at least four to 6 weeks prior to transplantation. Household members, close contacts and healthcare workers should also be carefully vaccinated. In general, live attenuated vaccines should be avoided in the transplant recipient and oral polio and poxvirus vaccines should not be administered to household contacts. In addition, vaccination within the first six months after transplantation may result in ineffective protection due to heavy immunosuppression [6].

Is the kidney transplant patient at increased risk for cancer?

Malignancies are responsible for up to one-third of deaths of kidney transplant patients. Age-appropriate cancer screening is recommended to all potential transplant recipients [6]. One of the most feared cancer complications is post-transplantation lymphoproliferative disorder and has been linked to immunosuppressive agent's ability to promote oncogenic viruses (Epstein-Barr Virus, CMV) replication. This entity is the most common malignancy in children and is the second most common malignancy in adults after skin cancer. Clinical manifestations include constitutional and localized symptoms of the gastrointestinal, respiratory tracts and the central nervous system [4]. Reduction or discontinuation of immunosuppressive therapy, particularly antilymphocyte antibody, cyclosporine, tacrolimus, and MMF is the first-line treatment. Another option is to convert from a calcineurin inhibitor to sirolimus which has a potent antiproliferative effect.

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RESUMEN

El manejo de los pacientes de trasplante renal representa, en la mayoría de los casos, un reto y requiere de un equipo multidisciplinario. El medico que trata estos pacientes debe tener amplios conocimientos en su manejo clínico, debido a que con mayor frecuencia se enfrentan con el cuidado a largo plazo de los mismos. La relación médico-paciente y accesibilidad, convierten al clinico en el eje del tratamiento, monitoreo y aplicación de medidas preventivas en el paciente de trasplante renal. Actualmente, la mayoría de los asuntos relacionados con el manejo de estos pacientes varía de acuerdo a cada centro de trasplante. Este artículo hace evidente la importancia de varios aspectos médicos dirigidos al clínico con el propósito de mejorar el reconocimiento y expandir conocimientos, con el desarrollo de un enfoque sistemático.

ABSTRACT

The kidney undergoes functional and structural changes during the aging process. The factors influencing these changes are currently under active investigation. The renal functional reserve is diminished in the elderly predisposing these individuals to the development of acute kidney injury when the balance of vasconstrictive and vasodilatory hormones are altered, particularly with medications. The development of acute kidney injury in the elderly portends a negative prognosis for the recovery of renal function. The management of end stage renal disease in the elderly is also a topic of intense discussion and clinical investigation. In this review, we explore the mechanisms responsible for the aging of the kidney. We also summarize the renal hemodynamic changes, urine and concentration and dilution alterations, and the changes in sodium and potassium metabolism associated with aging. The role and the consequences of dialysis treatment in the elderly are also explored in this review article.

Index words: *aging, kidney*

AGING AND THE KIDNEY

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INTRODUCTION

The interest in the study of chronic kidney disease (CKD) in the aging population parallels the rise in the incidence and prevalence of CKD in patients older than 70 years. The number of geriatric nephrology publications has dramatically increased in the last few decades with more than seven thousand publications from 2000 to 2009 (1). Moreover, the US Census Bureau projects a rise in the population over age 65 years from 39.4 million in 2010 to 69.4 millions in 2030. If CKD is defined as the presence of an estimated glomerular filtration rate (GFR) of 60 ml/min per 1.73 m2, the weigh prevalence of CKD in patients over 80 years old is close to 40% (2). Therefore, both internists and nephrologists must be cognizant of the potential impact of kidney disease in the aging population and develop practice guidelines that prevent the accelerated decline in renal function in this population.

The kidney develops functional and structural changes during the aging process. These changes may result in reduction in renal functional reserve predisposing to the development of acute kidney injury and alterations in the renal tubular reabsorptive and secretory processes. In this review, we will explore the mechanisms responsible for the aging kidney; summarize the renal hemodynamic changes, urine and concentration and dilution alterations, and the changes in sodium and potassium metabolism. Finally, we will also review the impact of dialysis treatment in the elderly and the use of maximum conservative management of ESRD patients when dialysis is not a reasonable treatment alternative.

Anatomic and Functional Changes in Aging

The renal mass increases from 50 grams at birth to 400 grams at age 20 but decreases to 300 grams in individuals between 80 to 90 years old (3). Human renal aging is characterized by the loss of renal cortical mass. Autopsy studies have shown a significant reduction in the total number of glomeruli per kidney in subjects older than 55 years when compared to younger individuals (4). Similar findings were reported in older kidney donors in a more recent study (5). The number of sclerotic glomeruli increases from 5% at age 40 to 10-30% in the eighth decade. The reduction in renal mass parallels the reduction in glomerular filtration rate. Both renal vascular resistance and filtration fraction increase with aging (6).

The focal segmental glomerular sclerosis (FSGS) type lesion associated to the aging process was studied in a detailed anatomic study performed in a group of elderly normotensive individuals that underwent unilateral nephrectomy due to tumors (7). These kidneys showed nonobstructive arteriolar hyaline deposits with associated dilation of the arteriolar lumen. The glomeruli associated to these dilated arterioles were hypertrophic. These findings resembled those that occur when autoregulation of the glomerular circulation is lost. The loss of autoregulation precedes the development of the FSGS-type lesion. There are also aglomerular arterioles in the renal cortex. The consequent rise in renal blood and filtration fraction of the juxtamedullary glomeruli may lead to glomerular hypertrophy. Moreover, atrophy of the peritubular capillaries leads to tubulointerstitial fibrosis (8). After 30 years of age, the glomerular filtration rate (GFR) declines at a rate of approximately 1 ml/year. This leads to a reduction of GFR by 20-25% after the fifth decade of life (9). The inulin clearance at age 90 years is around 65 ml/min (10)

The creatinine clearance decreases even though the serum creatinine level does not increase significantly in older patients without renal disease. This is mainly explained by a reduction in both creatinine production and urinary creatinine excretion from values of 20 mg/kg in individuals younger than 40 years old to less than 15 mg/kg after the fifth decade (11). The reduction in creatinine production and urinary excretion is explained by a concomitant reduction in total muscle mass in older individuals. There is controversy in the medical literature as to whether the reduction in GFR is part of the normal aging process or it is a consequence of other comorbid conditions (12).

The formulas to estimate GFR in the elderly should be used with caution since several studies have shown significant variations in the results when compared to the measured GFR. The Modification of Diet in Renal Disease (MDRD) equation performs better in patients with ages equal or above 65 years than in young subjects if the enzymatic method of creatinine determination is used (13). For instance, Fehrman and Skeppholm measured GFR with iohexal clearance and compared it with estimates using the MDRD and Cockroft-Gault equations in individuals with age range between 70 and 100 years (14). The measured mean GFR was 67.7 ± 10.8 ml/min. The MDRD equation estimated the GFR in 60.1 ± 11.8 ml/min but it was 46.2 ± 11.3 ml/min with the Cockroft-Gault equation. The MDRD equation also gives best estimates in patients with renal insufficiency.

Study	Years	Country	Dialysis	No. of Pts	Mean Age	12mo	Survival

Table 1: Comparison of studies evaluating different management strategies in elderly patient with ESRD

Molecular Basis of Renal Aging

There are several theories to explain the aging phenomena in the kidney. Genetic factors, telomere shortening and apoptosis and oxidative stress are among the culprits of renal senescence (12).

Telomere shortening occurs mainly in renal cortical cells with increasing age (15). There is an estimated 0.25% telomere shortening annually. Moreover, there is an increase in oxidative stress with aging. There is a correlation between oxidative stress and the advanced glycation end products (16). Increased oxidant stress has been described in age-associated chronic disease like diabetes mellitus, cardiovascular disease and chronic kidney disease (17). Oxidative stress is known to decrease the telomere length (18). There is also a reduction in renal endothelial nitric oxide synthetase expression with appearance of the enzyme in the tubular cells with aging (19). Interestingly, female rats have some protection for age-related renal damage (20). The renal cortical nitric oxide synthetase expression is maintained most likely due to the presence of estrogens.

The discovery of the gene that codifies a protein named 'klotho', in reference to the Greek goddess that spun the thread of life, opened a whole new field research in aging (21). A defect in the klotho gene expression in the mouse reduces dramatically the life span of the rodent. The syndrome also results in infertility, arteriosclerosis, skin atrophy and emphysema. The klotho gene encodes a transmembrane protein that interacts and forms a complex with fibroblast growth factor receptors. The klotho protein in then clipped on the cell surface and it is secreted into the bloodstream. It is possible that klotho serves as an endocrine factor. This circulating protein regulates the activity of multiple ion channels and growth factors including Insulin Growth factor -1 (IGF-1). Interestingly, the kidney is one of the organs with highest expression of klotho.

Changes in Electrolyte Balance in Healthy Elderly Patients

Total body water is reduced in aged patients due to less muscular mass proportion compared to body fat, but plasma and blood volume are maintained normal. Since elderly patients have reduced number of nephrons, their ability to dilute urine is impaired. Elderly have a decreased ability to tolerate both water deprivation and water boluses. The elderly have normal plasma antidiuretic hormone (ADH) levels but they have less responsiveness for ADH at the distal nephron that increases free water loss, and partially explains the prevalence of nocturia in old patients (22). In younger patients, ADH is released with diurnal variations, with increase secretion at night preventing nocturnal diuresis. These variations are absent in the elderly and they have lower nocturnal ADH than younger people.

Atrial natriuretic peptide (ANP) is increased five-fold over basal levels in the aged person. Also, the elderly exhibit an exaggerated increase in ANP in response to sodium chloride infusions. The effect of ANP to suppress aldosterone is exaggerated as well. ANP causes direct suppression of renin, which causes a decrease in angiotensin II and aldosterone that cause the kidney to lose sodium in the urine (22). This "salt wasting" tendency can exaggerate clinical hypovolemia when the old patient's capacity to conserve water and sodium is challenged by gastrointestinal losses of electrolytes. In the case of sodium deprivation or external sodium loss, the kidneys ability to minimize sodium excretion in urine is blunted in old patients.

Robert, et al (23) demonstrated in their animal study that old rats and young rats had the same consumption of water ad libitum; indicating similar thirst sensation, but old rats had impaired response to maintain water and sodium homeostasis after water and sodium deprivation. The ability of the elder to response to a sodium load also is reduced (24). This can be attributed to the reduction in GFR in the old kidney so sodium clearance takes longer. A large bolus of sodium can lead to extracellular volume expansion and hypernatremia due to mechanisms of free water loss and sodium retention because it takes longer for the patient to compensate.

Potassium balance also suffers some changes with age. Old patients not only have lower basal levels of aldosterone but also have a blunted response of aldosterone to increased potassium in plasma. Mulkerrin, Epstein and Clark concluded that healthy old patients had a lower increment in aldosterone levels after a potassium infusion when compared to their younger counterparts (25), which correlates with the fact that older patients are at increased risk of hyperkalemia, especially after taking certain medications or supplementations containing potassium. Some medications interfere with potassium excretion, among these are: ACE inhibitors, potassium-sparring diuretics, NSAIDs, Trimethoprim (26). Heparin inhibits aldosterone synthesis in the adrenal gland and ß-blockers interfere with intracellular potassium uptake thus increasing the risk of developing hyperkalemia. Also, tissue injury such as trauma or surgery also releases potassium into the blood stream and can be plasma infusion when compared to their young the trigger to hyperkalemia in the old patient (27).

Hypokalemia in the elderly population has been reported due to the higher prevalence of conditions such as hypertension or edematous disease, requiring medications that can induce hypokalemia (e.g. thiazide diuretics). Older people have less body potassium reserve since part of their muscular tissue has been replace by fatty tissue so older people have less effective compensation mechanisms for diuretic induce hypokalemia (28). Still, hypokalemia in healthy elderly is rare in the absence of these conditions. It is important to mention that gastrointestinal loss of potassium is a very important cause of hypokalemia in the elderly and should be carefully monitored in this population (29).

In elderly people, the pH is maintained in the normal range of 7.38-7.42, but this is achieved at the expense of a reduced bicarbonate (HCO_3) reserve. Studies indicate a progressive increase in the steady-state blood $[H^+]$ and a reduction in steady-state serum HCO_3 from subjects of increasing age. This means that old patients are in an incrementing age-related, low-level metabolic acidosis (30). Furthermore, old patients are less capable of counteracting a large acid load due to decrease renal excretion of acid and less bicarbonate reserve. The compensatory changes that the old patient develops to counter the chronic acidotic state may produce consequences such as nephrolithiasis, bone demineralization, and muscle protein breakdown. The presence of these maladaptive changes suggests that a "eubicarbonatemic" metabolic acidosis may exist in older patients and emphasizes the importance of recognition and treatment of even mild acid loads to prevent these maladaptive homeostatic responses.

A study from the American Heart Association indicates that for healthy aged people there is an increase in intracellular calcium, especially in platelets, and a decrease in extracellular calcium; which predisposes the subject to hypertension and insulin resistance (31). The elder's body compensates for the reduction in ionized calcium by increasing levels of PTH and 1, 25-alpha--dihydroxyvitamin D. Elder patients require more Vitamin D because of decrease exposure to sunlight and thus should receive supplementation to prevent calcium loss (32). Hypocalcemia cannot be normalized without correcting hypomagnesemia.

Toultou's study has indicated that there is high prevalence of magnesium deficiencies in the healthy elderly patient reflected by the erythrocyte magnesium concentration (33). The elderly have decreased renal reabsorption of magnesium in the renal tubules. Also healthy elders have an increased net endogenous acid production and according to Rylander, there is a correlation between the increased net endogenous acid production and increased urinary excretion of magnesium (34).

Serum phosphorus is an important measure of renal function. It is known to increase after reduction in a subject's GFR. In a study by Cirillo (35), demonstrated that old age is an independent factor for phosphorus retention and it is exacerbated by kidney disease in the old patient. This elevation in serum phosphorus in relationship to age was more significant in men; meanwhile women had different rates of serum phosphorus elevation that seemed to be dependent of menstrual status. Elevation in phosphorus leads to an elevation in parathyroid hormone. As discussed earlier, the elderly patient has various differences in renal function and electrolyte balance when compared to their younger counterparts. These differences must be taken into account when prescribing medication or selecting the appropriate treatment for this population. Physicians must also be alert of the possible triggers that can push a patient from having a compensated physiologic process to have an electrolyte imbalance that could increase the patient's morbidity and mortality.

Acute Kidney Injury in the Elderly

The risk of development of acute kidney injury (AKI) is high in elderly patients. Reports have described at least a three-fold increase in the incidence of AKI in patients older than 60 (36) or 70 years (37). The incidence of AKI has increased from 1996 to 2003 with a more marked rise in patients older than 80 years. The use of radiocontrast for imaging studies and increased susceptibility to drug-induced AKI are mentioned as possible factors for this rise (38). On the other hand, pre-renal and obstructive causes of AKI are particularly prevalent in the aging population (39). Use of some medications may predispose to the occurrence of pre-renal AKI. Of these, NSAID's seem to have a greater impact of renal hemodynamics in the elderly due to reduction in intrarenal vasodilatory prostaglandins. Its use is particularly prevalent in this age group (10-25%) (40). The preservation of GFR is more dependent on the vasodilatory effect of prostaglandins in the afferent arteriole in patients with CKD, Congestive Heart Failure, Diabetes Mellitus, and those taking diuretics or angiotensin converting enzyme inhibitors (ACEI's). The use of NSAID's increased the risk of pre-renal AKI by 13% in the elderly nursing home patients (41). Prompt discontinuation of the NSAID and expansion

of the extracellular fluid volume may prevent the further development of ischemic acute tubular necrosis in these patients.

The development of AKI in hospitalized patients with ages > 67 years results in an increased incidence of End Stage Renal disease (ESRD) (42). This rise was more prominent when the elderly patients had pre-existent CKD. The hazard ratio for developing ESRD was 41.2 for patients with AKI and CKD when compared to those without CKD. The development of AKI in this group of patients may be a contributory factor for the rise in the incidence of ESRD in these age groups.

Dialysis in the Elderly

The impact of initiation of hemodialysis on the functional status of elderly nursing home patients were studied by Kurella-Tamura and co-authors (43). Functional status was defined as the ability to perform basic activities as walking, bathing, getting out of bed, etc. A total of 3,702 nursing home residents of the national registry with a mean age of 73 years of age were initiated on hemodialysis between 1998 and 2000. The authors reported that three months after initiation of dialysis only 13 % had maintained the pre-dialysis functional status. A total of 58% of the dialysis patients died within the 12 months after initiation of therapy. They concluded that initiation of dialysis in nursing home residents was associated to a marked decline in functional status. The reasons for the elevated mortality rate during the first year of dialysis in patients over 80 years old is not completely clear but it is possible that the severity of the illness that caused the end stage renal failure may be the most significant prognostic factor (44).

A prognostic score for six-month mortality among elderly dialysis patients in the French Rein registry was recently reported (45). The overall six-month mortality of 2,500 patients age 75 years or older was 19% after initiation of dialysis. Interestingly, age was not associated with mortality during this short-term period. Nine clinical factors were used for the scoring system: body mass index, diabetes, congestive heart failure stages II and IV, peripheral vascular disease stages III and IV, dysrrytmia, active malignancy, severe behavioral disorder, total dependency for transfers, and unplanned dialysis. Mortality varied from 8% in the patients with the lowest score up to 70% in patients with the top score. The prediction of short-term prognosis with the use of this clinical scoring system may be of help in clinical decision making although the authors point out that it cannot be used to withhold dialysis.

Pre-dialysis counseling is essential in all patients but particularly in the elderly. The goals of the patient before initiation of dialysis must be clearly identified suggested by Arnold and Zeidel (46). The patient should also receive information about conservative management of the renal disease. Interestingly, 30% of patients older than 75 years of age withdraw from dialysis (47). Several negative prognostic factors in addition to older age have been identified in patients initiated on Hemodialysis. These include: reduced functional status, low body weight, severity and number of co-morbid conditions and late referral to the nephrologist (2, 48-49).

There are several published studies looking outcomes of older individuals that were treated conservatively versus those that were initiated on dialysis after developing end-stage renal disease. The data from three studies is summarized in table1. The survival of patients treated with dialysis or with conservative management is compared to the 12-month survival rate of all ESRD patients older than 80 years of age as reported in the United States Renal Data System report from 1996-2003. Survival rates at one year were lower in patients treated conservatively in the studies of Joly, et al (48) and Smith, et al (50) but were similar in the groups in the study of Murtagh, et al (51). The time of initiation of dialysis (early versus delayed) did not seem to impact survival rates at one year in the study of Brunori, et al. (52) from Italy. Nevertheless, the population studied was small and diverse clinical variables may be influencing these outcomes. Large prospective studies are required to define the population of elderly patients who would benefit from dialysis and those who would not.

The dialysis modality, peritoneal dialysis versus hemodialysis, seems to have an impact on patient outcome in the elderly population (44). A report in patients of ages at or above 65 years showed a 16 to 45% increased risk of death at one year among patients undergoing peritoneal dialysis when compared to a group of patients on hemodialysis (53). Similar findings were reported in a French study (54). In a more recent retrospective study of 1,613 patients older than 75 years who were started peritoneal dialysis, the median survival was 27.1 months (55). This study used the French Language Peritoneal Dialysis registry of patients on chronic ambulatory peritoneal dialysis or assisted peritoneal dialysis (treated at home with nurse assistance). The latter is fully covered by the national health care insurance in France.

Several special issues should be addressed before initiation of dialysis in an elderly patient. First, all the non-renal geriatric problems and co-morbidities should be evaluated and treated. Estimation of GFR is pivotal in determining when to refer the patient to a nephrologist. The goal of treatment of the renal disease is to improve function and quality of life rather than longevity (56). There should be sufficient time to create a vascular access before initiation of renal replacement therapy. The patients should have opportunities to execute advance directives. This document gives the patient the opportunity to help in the formulation of a long or short term plan for dialysis including the possibility of withdrawal from dialysis if the patient' goals are not achieved.

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RESUMEN

El riñón sufre cambios funcionales y estructurales con el proceso de envejecimiento. Los factores que influyen este proceso están en investigación. La reserva de función renal esta disminuida en el envejeciente, predisponiendo a estos individuos al desarrollo de fracaso renal agudo cuando las hormonas vasodilatadoras y

vasoconstrictoras son alteradas, en particular con medicamentos. El desarrollo de fracaso renal agudo en el envejeciente impacta negativamente el pronóstico de la recuperación de la función renal. El manejo de fracaso renal terminal en el envejeciente es tópico de discusión e investigación clínica intensa. En este repaso, exploramos los mecanismos responsables del envejecimiento del riñón. Además, se resumen los cambios en la hemodinámica renal, las alteraciones en concentración y dilución de la orina y los cambios en el metabolismo de sodio y potasio asociados al envejecimiento. El rol y consecuencias del tratamiento de diálisis en el envejeciente son también explorados en

DE LA LAVADORA AL RSP: Reseña de los comienzos de los servicios de hemodiálisis en el Hospital de Veteranos de San Juan

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RESUMEN

La invención del Dr. Willem Kolff revolucionó el tratamiento de los pacientes con enfermedad renal terminal en la década de los sesenta. Este logro coincidió con la aparición de la nefrología como subespecialidad. Un grupo de profesionales que incluían médicos, técnicos y enfermeras se dieron a la tarea de iniciar los programas de diálisis en los hospitales de Puerto Rico. El Hospital de Veteranos sirvió de centro de investigación y entrenamiento en estos primeros años de la hemodiálisis en la isla. Este artículo recoge los retos y esfuerzos genuinos de los profesionales que sentaron las bases de lo que conocemos hoy como la terapia de reemplazo renal.

Palabras claves: *lavadora, RSP, reseña, hemodiálisis, Hospital de Veteranos, San Juan*

IINTRODUCCION: Breve historia del desarrollo del riñón artificial

La máquina Kolff, mejor conocida localmente como la “lavadora” fue el primer riñón artificial práctico desarrollado durante la segunda guerra mundial (1943) por el médico holandés Willem Johan Kolff. En este equipo rudimentario original, se sangraba al paciente en un envase estéril y la sangre anticoagulada se pasaba por gravedad a un dializador rotativo hecho de membrana de celofán (la misma que se usaba en la confección de embutidos) que se sumergía en un tanque con la solución dializadora. La sangre pasaba por el dializador y era recogida en otro envase para ser devuelta al paciente también por gravedad.

En 1948 Kolff & Brigham modificaron el equipo original añadiéndole una bomba pulsativa para empujar la sangre del paciente al dializador y a la misma vez se aumentaban la superficie del dializador aumentando o disminuyendo el largo de la membrana. Para esta misma época Leonard Skeggs y Jack Leonards desarrollaron el primer dializador de flujo paralelo que por su diseño de membranas en hojas, tenía una resistencia baja al flujo de sangre y a su vez podían aumentar el área de superficie utilizando múltiples capas de membrana. Este diseño por la baja resistencia al paso de la sangre podía utilizarse sin bombas de sangre. Skeggs logró remover agua de la sangre en su riñón artificial creando un sifón en la salida del dializador, en lo que aparenta ser la primera referencia a presión negativa en diálisis.

En el 1956 Kolff y William B. Graham (CEO de Baxter) desarrollaron el primer dializador de membrana redonda (‘coil’) disponible comercialmente totalmente desechable conocido como el riñón anaranjado de Kolff. El dializador venía acompañado de líneas arterial y venosa. El volumen de cebado del dializador era de 1200-1400 ml, volumen que tenía que ser suplido por sangre donada, que se recogía al final del tratamiento y se refrigeraba hasta el próximo uso.

En 1960 salió al mercado el dializador tipo Kiil, desarrollado en Noruega por el Dr. Fred Kiil. Este usaba tres planchas de polipropileno con dos hojas de membrana de celulosa natural conocida como ‘cuprophan’, en cada plancha. La sangre entraba al dializador por portales externos de plástico adheridos a las membranas y el dializado se pasaba por el exterior de las membranas y en dirección opuesta a las planchas.

El exceso de fluido se removía usando presión negativa en la línea de salida del dializado. El volumen de cebado del Kiil era menos de 300 ml. En el 1964 salió al mercado el modelo Drake-Willock 4002 del dializador Kiil y fue manufacturado a nivel comercial acaparando el mercado internacional.

En 1964-1967, el doctor Richard Stewart recibió un endoso para estudiar la aplicación médica de fibras capilares hechas con acetato de celulosa. Su grupo de trabajo determinó que esa tecnología podía tener aplicación práctica como un riñón artificial al demostrar que sustancias y exceso de agua podían ser selectivamente removidos de la sangre.

Sus estudios lograron comprobar que las fibras capilares usaban un volumen menor de sangre y eran tan

eficientes como las membranas usadas en los dializadores de la época.

El modelo clínico de este dializador se usó por primera vez en la Universidad de Michigan y luego en la Escuela de Medicina de Marquette en Milwaukee. El dializador de fibra hueca se convirtió hasta el día de hoy en el dializador de predilección para la hemodiálisis.

En el 1967 la compañía Travenol de los laboratorios Baxter desarrolló el primer sistema integrado de diálisis para ser usado en hospitales y en el hogar. Lo llamaron el RSP (por sus siglas en inglés 'Recirculating Single Pass'). Esta máquina requería que se mezclaran las sales y químicos del dializado en un reservorio de 120 litros de agua y requería un periodo de tratamiento de seis horas. Usaba los dializadores tipo 'coil' desarrollados por Baxter y luego fueron modificadas para aceptar los filtros de fibra hueca.

Comienzos de la hemodiálisis en Puerto Rico

La hemodiálisis como la conocemos en la actualidad en Puerto Rico, comenzó en el Hospital Universitario departamento de Medicina del Centro Médico a mediados de la década del 1960 subvencionada con fondos de la Escuela de Medicina de la Universidad de Puerto Rico. Este proyecto fue posible mediante el esfuerzo conjunto de los doctores Roberto Rodríguez, Cristino Colón, Heriberto Morales y la asistencia técnica del Sr. Hiram A. Rivera. A este grupo luego se le unieron los doctores, Rafael Ramírez González, Hernán Padilla, Rafael Burgos Calderón, y el técnico, Sr. Tomás Irizarry. Más tarde se unió como consultor el Dr. Osvaldo Ramírez Muxó proveniente del Hospital de Veteranos localizado entonces en el sector de San Patricio.

El tratamiento en sus comienzos tomaba de seis a ocho horas dependiendo de la condición del paciente. Debido al alto costo de los materiales y las limitaciones físicas de la facilidad los servicios estaban restringidos a pacientes con condiciones agudas y algunos pacientes intoxicados con medicamentos u otros productos tóxicos.

Las primeras diálisis se hicieron con una máquina Kolff modificada que consistía de un tanque de acero inoxidable con capacidad de 100 litros en el cuál se disolvían los componentes químicos del dializado para formar una solución isotónica a la cual se le añadía glucosa para aumentar el gradiente osmótico y acido láctico para corregir el pH.

Se usaba un dializador tipo Kolff de doble membrana y se preparaba el dializado en la misma habitación del paciente. La máquina Kolff rindió su cometido por varios años más tenía varios inconvenientes. El dializado en el tanque se saturaba con la urea y otras substancias removidas de la sangre en el proceso y había que cambiarlo cada dos horas alargando así el tiempo total del tratamiento.

Para esta misma época se comenzaron a dializar pacientes en el hospital Auxilio Mutuo de Rio Piedras y en el hospital municipal de Ponce. En el hospital Auxilio Mutuo participaron los doctores Osvaldo Ramírez Muxó y Heriberto Morales, con la asistencia técnica de los señores Hiram Rivera y Tomás Irizarry, Sor Patrocinio González, Sra. Elisa Frades y la Sra. Lydia Cortés. En la primera diálisis en Ponce participaron los doctores Cristino Colón, Heriberto Morales, Jorge Gutiérrez y Ernesto Morales con la asistencia técnica del Sr. Hiram Rivera.

Bajo la supervisión del Dr. Heriberto Morales, los técnicos Hiram Rivera y Tomás Irizarry dializaron al reverendo padre René León por primera vez fuera del hospital, en su apartamento, convirtiéndose este en el primer paciente de diálisis en el hogar en la isla. Se utilizó una máquina diferente que había salido al mercado en aquella época conocida como RSP que había sido comprada por el paciente. El diseño de esta máquina permitía el tratamiento durante seis horas sin necesidad de remover el dializado. Debido a su versatilidad el RSP se convirtió en la máquina más utilizada en las unidades de diálisis existentes.

El tanque de polipropileno con capacidad para 120 litros de dializado contaba con una bomba de agua que lo circulaba a través de un medidor de flujo controlado a 320 ml/min hasta el recipiente de acero inoxidable donde se encontraba el dializador.

El dializado fresco se mezclaba con el saturado mientras recirculaba por el dializador y al mismo tiempo 320 ml del compartimiento se drenaban al sistema sanitario. El RSP serviría de eje más adelante para el desarrollo de la diálisis en el hogar.

Las primeras diálisis con el dializador tipo Kiil en el hospital Universitario fueron hechas gracias a las modificaciones, ajustes y cambios hechas por el Dr. Osvaldo Ramírez Muxó al sistema de bombeo de dializado y ya para mediados de la década del sesenta se logró comenzar un programa de diálisis para pacientes con condiciones crónicas en el Hospital Universitario de San Juan.

Inicio del Programa de Hemodiálisis en el Hospital de Veteranos

A principios del 1970 se comenzó un programa de hemodiálisis y diálisis peritoneal en el Hospital de Veteranos bajo la dirección del Dr. Osvaldo Ramírez Muxó. Su grupo de trabajo incluía al Dr. Rafael Ramírez González, los técnicos Hiram Rivera y Tomás Irizarry procedentes del Hospital Universitario. Frank González y Joyce Bou-Vierno fueron reclutados por el Dr. Ramírez en New York. El cuidado de enfermería de los pacientes estaba a cargo del Sr. Tomás Rivera y un pequeño grupo de enfermeras graduadas y asistentes de enfermería asignados por el departamento de enfermería del hospital, que fueron entrenados en las técnicas de diálisis por el Sr. Rivera y el Sr. Irizarry (ver Figura 1).

Uno de los componentes más importantes en todo sistema de diálisis en la actualidad es el tratamiento del agua.

Figura1: El Sr. Tomás Irizarry y la Sra. Marta Fernández, RN ensamblando un dializador tipo Kiil.

En los comienzos se utilizaba agua del grifo. Para la época en que se comenzó a dializar en el Hospital de Veteranos, la purificación del agua se hacía con deonizadores, más no habían llegado a la isla.

El Sr. Rivera y su grupo de técnicos utilizando su inventiva y los recursos disponibles en el hospital fabricaron los primeros filtros purificadores a base de cartuchos de carbón activado. Estos filtros se utilizaron hasta la construcción de la unidad de diálisis que incluyo un sistema de purificación de agua por deionización.

Las máquinas usadas para la época eran generadoras de presión negativa con los dializadores tipo Kiil, sin faltar un RSP para diálisis fuera de la unidad. Los dializadores Kiil fueron eventualmente desplazados por los RSP.

Esta época fue más que nada un continuo proceso de aprendizaje y trabajo arduo. No debemos olvidar que todas las soluciones se preparaban a mano y más tarde por sistemas semi-automáticos. Los dializadores tipo Kiil se preparaban a mano y se esterilizaban con formalina y las pruebas químicas, conductividad y osmolaridad eran esenciales para garantizar un dializado isotónico compatible con la sangre del paciente. Para esta época también la industria comenzaba a desarrollar nuevos dializadores y sistemas de diálisis y el hospital era uno de los centros de prueba de los manufactureros.

Accesos vasculares y la cánula externa Ramirez-Winged

La diálisis ha sido durante los pasados cincuenta años un proceso cambiante tanto en el aspecto clínico como en el tecnológico. Las máquinas, los dializadores, los accesos vasculares, los medicamentos, los métodos diagnósticos, todo ha evolucionado.

Tomemos como ejemplo, los accesos vasculares. Hoy tenemos fístulas arteriovenosas, catéteres Quintons, Tesios e injertos vasculares. A mediados del 1960 el Dr. Belding Scribner, de la Universidad de Washington en Seattle, le pidió a Wayne Quinton, un ingeniero biomédico, que le ayudara a desarrollar un acceso permanente al corriente sanguíneo de los pacientes renales. Scribner estaba convencido que podía dializar crónicamente a pacientes con fallo renal si conseguía un acceso permanente. Quinton desarrolló una cánula usando tubos de teflón con la cuál pudieron demostrar que si era posible dializar pacientes con enfermedad renal crónica utilizando un acceso vascular externo permanente.

Las cánulas externas se utilizaron por muchos años y fueron modificadas, incluyendo la conocida como Ramirez-Winged, de nuestro Dr. Osvaldo Ramírez Muxó. Si un paciente necesitaba diálisis con urgencia, no tenía que esperar por intervencional, ni pasar por la sala de operaciones. El Dr. Ramírez y sus discípulos le insertaban

la cánula localmente en un pequeño espacio de su oficina. Claro que para esa época todavía los médicos y las farmacéuticas no habían convertido a los cocos gram positivos en los demonios biológicos que tenemos hoy.

Con el paso del tiempo se desarrollaron técnicas quirúrgicas para unir arterias y venas convirtiéndose la fístula arteriovenosa como el acceso vascular ideal para la hemodiálisis.

Evolución de las maquinas de diálisis

Las máquinas de diálisis así como los dializadores han sido extensamente modificadas. Del sistema Kolff original pasamos a los dializadores tipo Kiil que tenían que ser ensamblados manualmente y esterilizados con formalina, tomando en consideración los riesgos que el uso de esta químico implicaba (ver Figura 2).

Figura 2: Visita del Dr. Hernán Padilla (Alcalde de San Juan) a la unidad de diálisis del Hospital De Veteranos en la celebración de la primera semana renal en la isla.

La salida al mercado de los dializadores tipo 'coil' usados en el sistema RSP encendió la inventiva de los Sres. Rivera e Irizarry que con la asistencia de la compañía 'Life Assist Medical Products' lograron la fabricación de contenedores plásticos para utilizarlos como equipo para diálisis. De esta manera se aumentaba de forma económica el número de máquinas de diálisis y por consiguiente un mayor número de pacientes por día.

De esta iniciativa no tardó mucho el mercado en lanzar a la calle los llamados "cannisters" claros, que luego evolucionaron hacia versiones más sofisticadas del RSP, que a su vez sentó la base para todo subsiguiente equipo de diálisis hasta nuestros días.

No podemos pasar por alto el más sofisticado de todos los sistemas, el sistema REDY. El sistema REDY recogió lo último en la tecnología y toda la gama de conocimiento en las técnicas de diálisis. Este sistema utilizaba solo seis litros de agua que no tenía que ser purificada ya que el sistema proveía un cartucho compuesto de varias capas de agentes químicos que purificaban el agua y la regeneraba eliminando los desperdicios tóxicos de la diálisis. El sistema era extremadamente costoso, lo que limitaba su uso.

Hospital de Veteranos como centro de entrenamiento en diálisis

En el Hospital De Veteranos fueron muchas las personas entrenadas en las técnicas de diálisis incluyendo médicos, técnicos y enfermeras. No solo se entrenaron personas del área metropolitana sino también de otros pueblos de la isla. También se entrenaron médicos, técnicos y enfermeras de St. Thomas, Santa Cruz y otros países del Caribe. Todo aquel ya sea técnico, enfermera o médico que haya estudiado nefrología en Puerto Rico, ha aprendido las técnicas de diálisis de mano de alguien que en sus raíces fue discípulo del Sr. Hiram Rivera. El Dr. Ramírez Muxó afirmaba que "para tener un buen entrenamiento en nefrología y diálisis todos tenían que mojarse las manos" y la mejor forma era con los técnicos de diálisis.

El grupo de técnicos de diálisis lo componían el Sr. Hiram Rivera, supervisor, Tomás Irizarry, Luis Cruz, Frank González, Carlos Torres, Francisco Gracia, Francisco Aguirre, Carmelo Rivera, Carmelo López, José L. Rodríguez y Héctor Jiménez (ver Figura 3).

La inventiva local y expansión del programa de diálisis

Este grupo de técnicos entrenados por el Sr. Rivera y el Dr. Ramírez Muxó fue partícipe del crecimiento y desarrollo de la unidad de diálisis del hospital. Las

Figura 3: El Dr. Ramírez Muxó acompañado de parte del grupo original de la Unidad de Diálisis del Hospital De Veteranos.

paredes de la oficina del supervisor estaban llenas de certificados de reconocimiento y sobre todo de certificados de sugerencias que cambiaron las técnicas de diálisis tanto en principios como en teoría.

Las muertes en diálisis por embolias de aire debido a la salina en botellas de vidrio fueron eliminadas gracias a que el Sr. Rivera se inventó un aditamento con una bolsa plástica que por diferencias en presión de aire evitaba que la botella se vaciara, evitando así las embolias por aire. A pesar de haber sido el invento bautizado por los técnicos con un nombre producto de la experiencia de trabajo (que por razones de la ley HIPPA no podemos publicar) este no fue nunca patentizado, pero fue la base para la fabricación de solución salina en bolsas de plástico por una industria médica del país.

Otras de las aportaciones del grupo de técnicos fue el concepto de hacer diálisis en seco, que nos daba la capacidad de remover grandes cantidades de fluido del sistema sanguíneo sin inducir la inestabilidad hemodinámica que la ultrafiltración por diálisis causa en el paciente. También se desarrollaron sistemas para oxigenar la sangre durante el tratamiento y sistemas para hacer cambios de sangre a pacientes intoxicados con sustancias no dializables.

De la misma forma se modificaron las líneas, dializadores, la composición y concentración del dializado para hacer posible la primera hemodiálisis pediátrica que se hizo en la isla en un infante de dos años de edad.

Se desarrolló también el primer sistema de plasmaféresis, que se mantiene aún como uno de los pocos programas de féresis clínica en la isla.

Es bueno recordar que muchas de estas contribuciones al desarrollo de la hemodiálisis, pasaron desapercibidas ya que en el sistema federal los inventos y contribución intelectual del empleado pertenecen a la institución y por lo tanto no pueden ser patentizados. El empleado solo recibe un pergamino y con un poco de suerte alguna consideración económica.

A mediados de la década del setenta se comenzaron a dializar en el hospital pacientes de la comunidad, aunque no recordamos si hubo una directriz local escrita sobre el tratamiento a pacientes no veteranos, si sabemos que hubo acuerdos mutuos para ofrecer los servicios. No debemos olvidar que la unidad del Hospital Universitario contaba con solo cuatro estaciones y posiblemente no daba a basto. El Dr. Ramírez Muxó, tomó la iniciativa y obtuvo la aprobación de la Administración de Veteranos para este proyecto con la salvedad de que los pacientes de la comunidad recibieran los mismos servicios que recibían los pacientes veteranos en diálisis. No era cuestión de dializarlos solamente, el seguimiento, los medicamentos y demás

servicios ancilares tenían que estar incluidos.

El tratamiento en casos especiales y las féresis, se justificaba como ayuda humanitaria por no haber suficientes facilidades fuera del Hospital de Veteranos. Cuando se comenzó el programa de trasplante renal, se autorizó a trasplantar a no veteranos porque el servicio era de el Programa de Trasplante Renal de Puerto Rico que estaba localizado en el Hospital de Veteranos.

Era en nuestro hospital donde existía el profesional experto, el equipo y la tecnología requerida para el éxito del mismo. Diálisis a estos pacientes se administraba en apoyo al programa. Se dializaban en preparación al trasplante y post trasplante hasta que el injerto funcionaba o cuando ocurría rechazo.

Para esta época también el sistema de salud del Departamento Del Veterano había cambiado sus normas y todo veterano ya fuera o no su condición conectada con el servicio militar tenía derecho a recibir el tratamiento de hemodiálisis. Como era de esperarse la población de pacientes sufrió un incremento substancial.

De dos turnos de pacientes con que comenzamos pasamos a 24 horas de servicio. El último turno terminaba a las cuatro de la madrugada y el primero comenzaba a las seis de la mañana y aún así no dábamos a basto.

Para dar servicio a toda la población se instituyó el programa de diálisis en el hogar, que fue concebido, diseñado e implantado por el Dr. Ramírez Muxó como un servicio al paciente que le facilitaba el acceso al tratamiento y le ayudaba a rehabilitarse y desarrollar independencia.

El programa comenzó con el entrenamiento por el grupo de técnicos bajo el liderato del Sr. Tomás Irizarry, de la Sra. Ana Prieto RN y más adelante con el técnico Carmelo López como técnico designado permanente al programa.

Programa de diálisis en el hogar y trasplante renal

Gracias a los avances tecnológicos de los equipos y dializadores y luego de un adecuado y bien supervisado entrenamiento se hacía posible que el tratamiento podía realizarse en la comodidad del hogar con seguridad.

El programa de diálisis en el hogar fue uno de los más exitosos en la historia de nuestra unidad y llegó a tener en sus inicios cerca de cincuenta pacientes dializándose en el hogar. El programa comprendía todos los aspectos del tratamiento. Las esposas/esposos o familiar eran entrenados en la unidad en todos los aspectos de las técnicas de diálisis.

Los técnicos diseñaban el espacio físico en el hogar del paciente y el hospital lo construía de acuerdo a sus especificaciones. Se les instalaba el equipo, el sistema de purificación de agua y se le daba seguimiento tanto médico, social, técnico y dietético con visitas frecuentes.

La Sra. Prieto estuvo por diez y seis años al frente del programa, al retirarse dejó treinta y seis pacientes dializándose en el hogar, habiendo entrenado en total un centenar de pacientes tanto veteranos como pacientes de la comunidad.

Con la llegada de la cubierta de las condiciones renales terminales por Medicare, y el subsiguiente desarrollo de unidades de diálisis privadas, la población de pacientes renales en el hospital mermó y de la misma forma el programa fue desapareciendo ya que la unidad podía absorber los pacientes del hogar.

La mejor evidencia del éxito del programa de diálisis en el hogar, la tenemos en el veterano Carmelo Rivera y su esposa Amparo que está n próximos a celebrar tres décadas de diálisis en su hogar de Bayamón.

Además de la diálisis en el hogar se inició en el Hospital de Veteranos el primer programa de trasplante renal en la isla. Bajo la dirección del Dr. Eduardo Santiago Delpín y su grupo de trasplante, se hizo el domingo 10 de Septiembre de 1978 el primer trasplante de riñón en la isla. Este programa se mudó al hospital Auxilio Mutuo más adelante donde permanece cosechando éxitos y devolviendo salud a la población renal en general (ver Figura 4).

El programa de diálisis renal, diálisis peritoneal, diálisis en el hogar y el programa de un exitoso entrenamiento en nefrología del Hospital de Veteranos fueron obra de la iniciativa, liderazgo y la visión del Dr. Ramírez Muxó.

Figura 4: El Dr. Santiago Delpín y parte de su grupo de trasplante renal en el Hospital de Veteranos

Primera unidad de diálisis en la comunidad

La primera unidad privada de servicios a la población con fallo renal, la estableció el Dr. Ramírez Muxó en la calle Duarte del sector Cantera de Hato Rey, con la participación del Sr. Tomas Irizarry, quien entrenó cerca de 150 técnicos y enfermeras en las técnicas de hemodiálisis.

La unidad contaba con veinte estaciones de diálisis y se hizo bajo los auspicios económicos de 'Biomedical

Applications', una corporación con base en Estados Unidos y que más adelante cambiaria de dueños hasta lo que conocemos hoy como 'Fresenius Medical Care'.

Ley reglamentadora de los profesionales de diálisis

En el 1978 ya se veía el crecimiento acelerado de los servicios de diálisis en la isla. El Sr. Tomás Irizarry, uno de los técnicos pioneros en los servicios de diálisis tomó la encomienda de conseguir que la práctica de esta nueva profesión fuera reglamentada.

Con su propio esfuerzo logró que la legislatura del país pasara legislación sobre ese particular. La ley número 188 aprobada en Julio del 1979 establecía "los mecanismos de reglamentación gubernamental para garantizar la excelencia en el cuidado renal, manteniendo y restaurando la salud renal dentro del alcance humano y evitando el uso de personal sin la capacidad profesional necesaria para bregar con la misma", según se establece en la exposición de motivos de la ley. La legislación comprendía los requisitos mínimos que debían tener los nuevos profesionales prestando servicios de diálisis y creaba una junta examinadora y certificadora. La junta hizo su primera prueba de certificación, en la que participaron los técnicos y enfermeras que para esa época estaban practicando la profesión, resultando en la certificación de la mayoría.

La ley estuvo vigente hasta el 2008 y por razones que los auspiciadores solo conocen, la asamblea legislativa pasó la ley número 214 del 2008, derogando la ley anterior.

En la actualidad la práctica de esta especialidad está huérfana de reglamentación, a pesar que a nivel federal desde el 2010 todos los técnicos de diálisis deben estar certificados y es de esperarse que en un futuro no muy lejano los profesionales de enfermería ejerciendo esta labor técnica también lo estén.

Nuevos retos en el tratamiento de diálisis

La realidad es que gracias a los adelantos tecnológicos en el campo de los sistemas de diálisis, se ha hecho extremadamente fácil la técnica de dializar a un paciente. Cada unidad privada entrena a sus enfermeras en la conexión del acceso vascular del paciente al sistema extracorpóreo, lo demás es programar la máquina y ya tenemos un profesional de diálisis en función.

En la isla hay aproximadamente 4000 personas con enfermedad renal terminal. Los centros de servicios privados se concentran en las zonas urbanas principales y los pueblos limítrofes a estas áreas, dejando a la mayor parte de la población renal especialmente a los del centro de la isla y pueblos pequeños a la deriva. Solo un paciente renal puede decir lo difícil que le resulta lograr llegar hasta los centros de servicios renales. La cubierta por Medicare de los servicios renales es uno de los gastos mayores del sistema y últimamente han terminado el pago de la transportación de pacientes a los centros renales. Los legisladores y el departamento de salud de la isla debían de tomar cartas en el asunto y derogar los reglamentos y requisitos para al establecimiento de unidades de diálisis privadas en la isla que en la actualidad solo benefician a unos pocos.

El 11 de Febrero del 2009 murió el investigador médico Dr. Willem J. Kolff, inventor de la máquina del riñón artificial para diálisis. El Dr. Kolff nunca patentizó su máquina de diálisis que ha sido perfeccionada de manera tal que se calcula que en los Estados Unidos cerca de 60,000 y cerca de 4000 en Puerto Rico, pacientes con enfermedad renal terminal, se mantienen vivos por su invento o las subsiguientes modificaciones de este. Este investigador prodigioso dejó su país natal Holanda y llegó a Estados Unidos dónde dirigió el equipo que inventó, probó y patentizó por primera vez un corazón artificial.

La innovación en cualquier campo del saber humano emana del poder inquisitivo de nuestra mente. El profesional completo es aquél que piensa más allá de lo enseñado por los maestros y los libros de texto.

El Dr. Kolff poseedor de nueve doctorados honoríficos fue exaltado al salón de la fama de los inventores en el 1985. Con su fallecimiento termina para la nefrología la época del investigador médico técnico, aquel que no conforme con el entendimiento clínico de la enfermedad dedica su conocimiento, su esfuerzo y los recursos que le provee su profesión, para encontrar soluciones en la tecnología. Soluciones que puedan hacer la diferencia, y que lleven a eliminar el concepto de enfermedad terminal en el diagnóstico de nuestros pacientes renales.

Ese ejemplo del Dr. Kolff lo recibimos el grupo de tecnólogos de hemodiálisis del Hospital de Veteranos de manos del Dr. Osvaldo Ramírez Muxó, quien siempre tendrá la admiración y nuestro eterno agradecimiento.

Reconocimiento

Este artículo fue redactado gracias al insumo de tres pioneros de la diálisis en Puerto Rico: El Sr. Hiram Rivera, el Sr. Tomas Irizarry y el Dr. Rafael Ramírez González.

ABSTRACT

The invention of Dr. Willem Kolff revolutionized the treatment of the patients with end-stage renal disease in the sixties. This milestone coincided with the beginning of nephrology as a medical subspecialty. A group of professionals that included physicians, technicians and nurses took the task of initiating the first dialysis programs in the hospitals of Puerto Rico. The Veterans Hospital served as a research and training center during the first years of hemodialysis in the island. This article summarizes the challenges and genuine efforts of the professionals that built the foundation of what we know today as renal replacement therapy.

Picture This

REACH FOR A HIGHER CONCENTRATION OF GATIFLOXACIN

Introducing gatifloxacin at a newly elevated 0.5% formulation that maintains the safety and tolerability you've come to expect[1]

INTRODUCING

ZYMAXID™
(gatifloxacin ophthalmic solution) 0.5%

Reach Higher

INDICATION

ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% is a topical fluoroquinolone anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: *Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis* group,* *Streptococcus oralis,** and *Streptococcus pneumoniae*.

*Efficacy for this organism was studied in fewer than 10 infections.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

ZYMAXID™ solution should not be introduced directly into the anterior chamber of the eye. As with other anti-infectives, prolonged use of ZYMAXID™ may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis or during the course of therapy with ZYMAXID™.

ADVERSE REACTIONS

The most frequently reported adverse reactions occurring in ≥ 1% of patients in the gatifloxacin study population (N = 717) were: worsening of the conjunctivitis, eye irritation, dysgeusia, and eye pain. Additional adverse events reported with other formulations of gatifloxacin ophthalmic solution include chemosis, conjunctival hemorrhage, dry eye, eye discharge, eyelid edema, headache, increased lacrimation, keratitis, papillary conjunctivitis, and reduced visual acuity.

Please see brief summary of full prescribing information on adjacent page.

1. ZYMAXID™ Prescribing Information.

ZYMAXID™
(gatifloxacin ophthalmic solution) 0.5%

ALLERGAN

BRIEF SUMMARY

Sterile

INDICATIONS AND USAGE

ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-Positive Bacteria:
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus mitis group*
*Streptococcus oralis**
Streptococcus pneumoniae

Aerobic Gram-Negative Bacteria:
Haemophilus influenzae

*Efficacy for this organism was studied in fewer than 10 infections.

DOSAGE AND ADMINISTRATION

Patients 1 year of age or older: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1. Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Topical Ophthalmic Use Only

ZYMAXID™ solution should not be introduced directly into the anterior chamber of the eye.

Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use of **ZYMAXID**™ (gatifloxacin ophthalmic solution) 0.5% may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and where appropriate, fluorescein staining.

Avoidance of Contact Lens Wear

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis or during the course of therapy with **ZYMAXID**™ (see **PATIENT COUNSELING INFORMATION**).

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies with **ZYMAXID**™, the most frequently reported adverse reactions occurring in ≥ 1 % of patients in the gatifloxacin study population (N=717) were: worsening of the conjunctivitis, eye irritation, dysgeusia, and eye pain.

Additional adverse events reported with other formulations of gatifloxacin ophthalmic solution include chemosis, conjunctival hemorrhage, dry eye, eye discharge, eyelid edema, headache, increased lacrimation, keratitis, papillary conjunctivitis, and reduced visual acuity.

DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with **ZYMAXID**™ ophthalmic solution.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic Effects: There were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day (approximately 1000-fold higher than the maximum recommended ophthalmic dose). However, skeletal/craniofacial malformations or delayed ossification, atrial enlargement, and reduced fetal weight were observed in fetuses from rats given ≥150 mg/kg/day (approximately 3000-fold higher than the maximum recommended ophthalmic dose). In a perinatal/postnatal study, increased late post-implantation loss and neonatal/perinatal mortalities were observed at 200 mg/kg/day (approximately 4000-fold higher than the maximum recommended ophthalmic dose).

Because there are no adequate and well-controlled studies in pregnant women, **ZYMAXID**™ solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **ZYMAXID**™ is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of **ZYMAXID**™ in infants below one year of age have not been established. **ZYMAXID**™ has been demonstrated in clinical trials to be safe and effective for the treatment of bacterial conjunctivitis in pediatric patients one year or older.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

PATIENT COUNSELING INFORMATION

Avoiding Contamination of the Product

Patients should be instructed to avoid contaminating the applicator tip with material from the eye, fingers, or other source.

Avoidance of Contact Lens Wear

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

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CME Questions

Questions from article entitled: ” ENFERMEDAD RENAL PERMANENTE EN PUERTO RICO: INCIDENCIA, PREVALENCIA Y MORTALIDAD DE 2000 – 2008”, by Ylene D. Rodríguez Ortiz MS, Glenda Miranda MD, Rafael Burgos Calderón MD, Santos Depine MD3, Otegbola Ojo MBBS.

1. La principal causa de la ERP en Puerto Rico es:
A) Hipertensión
B) Glomérulonefritis
C) Diabetes Mellitus Tipo 2
D)Riñones Poliquísticos

2. La mayoría de los pacientes recibiendo tratamiento en Puerto Rico se encuentran entre las edades de:

A) 40 – 50 años
B) 70 – 80 años
C) 30 – 40 años
D) 50 – 79 años

3. El país con mayor incidencia de ERP a nivel mundial debido a la Diabetes Mellitus es:

A) México
B) Taiwán
C) EEUU
D) Puerto Rico

Questions from article entitled: “LIFE THREATENING HYPERKALEMIA IN CHRONIC KIDNEY DISEASE PATIENTS TREATED WITH TRIMETHOPRIM-SULFAMETHOXAZOLE: A Case Series”, by Ricardo Calderón-Ortiz MD, Pedro Colton-Verge MD, Myrna Muñiz-Ortega MD, Laura Lespier MD, and Héctor Córdova MD.

4. Trimethoprim-Sulfamethoxazole decreases the kidney’s ability to excrete:

A) sodium
B) potassium
C) calcium
D) magnesium
E) chloride

5. Due to this effect of Trimethoprim-Sulfamethoxazole, patients with chronic kidney disease are at risk of developing clinically significant:

A) hypernatremia
B) hyperkalemia
C) hypercalcemia
D) hypermagnesemia
E) hyperchloremia

6. The main stimuli for potassium excretion by the distal nephron are:

A) tubular fluid flow
B) amount of sodium delivered to the principal cell of cortical collecting duct
C) aldosterone effect on the same tubular cell
D) all of the above
E) none of the above

Questions from article entitled:” HOPEFUL WAITING: Positive Outcome of Blood Pressure Monitoring in an Emergency Department”, by Wilfredo Eddy Bravo Llerena MD, David Claudio PhD, José Ramírez Rivera MD

7. One of the major problems of modern hospital triage system is:

A) The process of sorting patients into groups based on the perceived need for immediacy of medical treatment.
B) The usual monitoring of patients’ vital indicators while waiting in an ED.
C) Its failure to promptly detect patients’ vital signs changes and clinical deterioration during ED waiting time.
D) The complete absence of new ideas for bettering such system.

8. Several studies have shown that while waiting in an ED:

A) Patients with chronic cardiovascular and pulmonary diseases are not prone to deterioration.
B) Patients experience a heightened physiologic response and elevated catecholamine levels.
C) Pain, anxiety, lack of information, and feelings of helplessness, distrust and fear do not play an important role in patients’ final clinical outcome.
D) Periodical monitoring of patients’ vital indicators is completely useless.

9. All of the following can be concluded out of this stu dy, except:

A) BP monitoring every 30 minutes improves patients’ clinical outcome while waiting in an ED.
B) BP monitoring every 30 minutes of ED waiting patients should be implemented.
C) BP monitoring every 30 minutes of ED waiting patients is a simple approach.
D) Monitoring of oxygen, body temperature, pulse and respiratory rate in ED waiting patients yields useful information for determining the need of increasing their medical priority.

Questions from article entitled: “PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A rare acquired hematologic disorder”, by Mónica Santiago Casiano MD, Liza M. Paulo Malavé MD, Omayra González Rodríguez MD, William Cáceres MD.

10. The etiology of paroxysmal nocturnal hemoglobinuria (PNH) is:

A) Warm autoantibodies against red blood cell
B) Activation of blood proteases
C) Defect in glycophosphatidyl inositol anchored proteins in stem cells
D) Agglutinins that precipitate at cold temperatures
E) Proliferation of glomerular mesangial cells

11. The most accurate test for the diagnosis of PNH is:

A) Direct and indirect Coombs test
B) Ham’s test
C) Sugar water test
D) CD55/CD59/CD14 expression by flow cytometer
E) ADAMST-13 levels

12. The best available treatment for the hemolysis in PNH is:

A) Eculizumab (Soliris)
B) Blood transfusions
C) Cyclophosphamide
D) Danazol
E) Warfarin

Questions from article entitled: “PRIMARY ANGIOSARCOMA OF THE BREAST IN A PRE-MENOPAUSAL WOMEN”, by Mónica Santiago Casiano MD, Sharon Pagán Pagán MD, Luis Báez MD, William Cáceres Perkins MD, Rafael Ramírez Weiser MD, José Hernán Martínez MD, Daniel Conde Sterling.

13. Primary angiosarcoma is the most common malignancy affecting the breasts. TRUE or FALSE?

A) True
B) False

14. The treatment of choice for localized primary angiosarcoma of breast is: A) Surgery
B) Chemotherapy
C) Hormones
D) Aromatase inhibitors
E) Irradiation

15. Sites of metastases of primary angiosarcoma of the breast include:

A) Lungs
B) Skin
C) Liver
D) Bone
E) All of the above

Questions from article entitled: “KIDNEY TRANSPLANTATION AS TREATMENT FOR END STAGE RENAL DISEASE”, by Eduardo Santiago-Delpín MD.

16. The most common causes of end-stage renal disease in Puerto Rico are:

A) glomerulonephritis
B) pyelonephritis
C) diabetes
D) hypertension
E) c and d

17. Absolute contraindications for renal transplantation continue to be:

A) generalized cancer
B) generalized infection
C) untreatable cardiac or cerebrovascular disease,
D) untreatable liver disease
E) all of the above

18. The most common cause of organ loss after renal transplantation is/are:

A) chronic immunosuppression
B) chronic allograft nephropathy
C) chronic rejection
D) all of the anove
E) none of the above

Questions from article entitled: “AGING AND THE KIDNEY”, by Eddie M. Rodríguez-Castro MS, Héctor R. Córdova MD.

19. There are several theories to explain the aging phenomena in the kidney. They include:

A) Genetic factors
B) telomere shortening
C) apoptosis
D) oxidative stress
E) all of the above 20. Total body water is reduced in aged patients due to less muscular mass proportion compared to body fat, but plasma and blood volume are maintained normal. This concept is TRUE or FALSE?

A) True
B) False

21. The dialysis modality, peritoneal dialysis versus hemodialysis, seems to have an impact on patient outcome in the elderly population . A report in patients of ages at or above 65 years showed a 16 to 45% increased risk of death at one year among patients undergoing hemodialysis when compared to a group on peritoneal hemodialysis. This concept is TRUE or FALSE?

A) True
B) False

Boletin 103:3, 2011 - CME Answers

1.	A	B	C	D
2.	A	B	C	D
3.	A	B	C	D
4.	A	B	C	D
5.	A	B	C	D
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17.	A	B	C	D
18.	A	B	C	D
19.	A	B	C	D
20.	A	B	C	D
21.	A	B	C	D

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_____ Nombre del padre _____ Nombre de la madre _____ Nombre del conyuge

Entrenamiento

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Hasta ____ ____ ____ (DIA MES AÑO)

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1:45 - 2:00 pm	Preguntas y Respuestas
2:00 – 2:45 pm	**TRATAMIENTO DEL INFARTO AGUDO DEL MIOCARDIO** **Puerto Rico Infarction National Collaborative Experience (PRINCE)** Dr. José Novoa Loyola: Medicina Interna y Cardiologia
2:45 - 3:00 pm	Preguntas y Respuestas
3:00 – 3:15 pm	Receso
3:15 – 4:00 PM	**HIGADO GRASO**: Diagnostico, Prevención y Tratamiento. Dr. Melvin Meléndez: Medicina Interna y Gastroenterología.
4:00 - 4:15 pm	Preguntas y Respuestas
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5:00 - 5:15 pm	Preguntas y Respuestas:
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Important Safety Information for Humalog

Contraindications

- Humalog® is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.

Warnings and Precautions

- **Dose Adjustment and Monitoring:** Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously. Concomitant oral antidiabetic treatment may need to be adjusted.

  The time course of action for Humalog may vary in different individuals or at different times in the same individual and is dependent on many conditions, including delivery site, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require insulin dose adjustment.

- **Hypoglycemia:** Hypoglycemia is the most common adverse effect of Humalog. The risk of hypoglycemia increases with tighter glycemic control. Educate patients to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia. Severe hypoglycemia may be life threatening and can cause seizures or death.

  Use caution in patients with hypoglycemia unawareness and who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value.

  Timing of hypoglycemia usually reflects the time-action profile of administered insulins. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may alter the risk of hypoglycemia.

- **Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog.

- **Hypokalemia:** Humalog can cause hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).

Important Safety Information for Humalog, continued

Warnings and Precautions, continued

- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

- **Mixing of Insulins:** Humalog for subcutaneous injection should not be mixed with insulins other than NPH insulin. If Humalog is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing.

- **Subcutaneous Insulin Infusion Pump:** Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.

  Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with Humalog may be required. Train patients using an insulin pump to administer insulin by injection and to have alternate insulin therapy available in case of pump failure.

- **Drug Interactions:** Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required.

Adverse Reactions

- Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

Use in Specific Populations

- **Pediatrics:** Humalog has not been studied in children with type 1 diabetes less than 3 years of age or in children with type 2 diabetes.

Dosage and Administration

- Humalog should be given within 15 minutes before or immediately after a meal.

Please see following pages for Brief Summary of Full Prescribing Information for Humalog.

HI HCP ISI 08JUN2011

Humalog®

insulin lispro injection (rDNA origin)

Paradigm REAL-Time Revel™ MiniMed

MiniMed Paradigm REAL-Time Revel Insulin Pump Indications for Use

Pump

The Paradigm Revel insulin pump is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.

MiniMed Paradigm REAL-Time Revel Insulin Pump Important Safety Information

Contraindications

Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day and to maintain contact with their healthcare professional. Successful insulin pump therapy requires sufficient vision or hearing to allow recognition of the pump signals and alarms.

Warnings

The pump is not suitable for use in the presence of a flammable anaesthetic mixture with air, oxygen or nitrous oxide.

Standard Luer sets are not compatible with the Medtronic MiniMed Paradigm pump. Medtronic Diabetes Paradigm reservoirs and Paradigm-compatible infusion sets are specifically designed for use with the pump.

Do not modify your Paradigm reservoir or Paradigm-compatible infusion set.

Do not put any other drugs/medications inside your reservoir to use with this pump. Only insulin that has been prescribed by your physician can be used in this pump.

Do not use pump cases that have a magnetic clasp.

Do not expose your insulin pump to MRI equipment or other devices that generate very strong magnetic fields. The magnetic fields in the immediate vicinity of these devices can damage the part of the pump's motor that regulates insulin delivery, possibly resulting in over-delivery and severe hypoglycemia. Your pump must be removed and kept outside the room during magnetic resonance imaging (MRI) procedures.

If your pump is inadvertently exposed to a strong magnetic field, discontinue use and contact our 24 Hour HelpLine for further assistance.

Please visit http://www.medtronicdiabetes.com/about/safety.html for complete safety information.

The MiniMed Paradigm Revel Insulin Pump does not include optional continuous glucose monitoring (CGM) technology available from Medtronic Diabetes. For information on the MiniMed Paradigm Revel Insulin Pump integrated with CGM, please contact your Medtronic Diabetes representative.

Please see Important Safety Information for Humalog on opposite page.

Medtronic

Lilly

Humalog®

(insulin lispro injection [rDNA origin])

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

HUMALOG is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS

HUMALOG is contraindicated:

- during episodes of hypoglycemia
- in patients who are hypersensitive to HUMALOG or to any of its excipients.

WARNINGS AND PRECAUTIONS

Dose Adjustment and Monitoring—Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for HUMALOG may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

Hypoglycemia—Hypoglycemia is the most common adverse effect associated with insulins, including HUMALOG. The risk of hypoglycemia increases with tighter glycemic control. Patients must be educated to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may be different for each person and may change from time to time. Severe hypoglycemia can cause seizures and may be life-threatening or cause death.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia *[see Drug Interactions]*.

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers *[see Drug Interactions]*, or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Hypersensitivity and Allergic Reactions—Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMALOG *[see Adverse Reactions]*.

Hypokalemia—All insulin products, including HUMALOG, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Renal or Hepatic Impairment—Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Mixing of Insulins—HUMALOG for subcutaneous injection should not be mixed with insulin preparations other than NPH insulin. If HUMALOG is mixed with NPH insulin, HUMALOG should be drawn into the syringe first. Injection should occur immediately after mixing.

Do not mix HUMALOG with other insulins for use in an external subcutaneous infusion pump.

Subcutaneous Insulin Infusion Pumps—When used in an external insulin pump for subcutaneous infusion, HUMALOG should not be diluted or mixed with any other insulin. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days. HUMALOG should not be exposed to temperatures greater than 98.6°F (37°C).

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with HUMALOG may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure *[see Dosage and Administration and How Supplied/ Storage and Handling]*.

Drug Interactions—Some medications may alter insulin requirements and the risk for hypoglycemia or hyperglycemia *[see Drug Interactions]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions]*.
- Hypokalemia *[see Warnings and Precautions]*.

Clinical Trial Experience—Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared with those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of Treatment-Emergent Adverse Events during HUMALOG clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=81)	Regular human insulin (n=86)	Total (n=167)
Flu syndrome	28 (34.6)	28 (32.6)	56 (33.5)
Pharyngitis	27 (33.3)	29 (33.7)	56 (33.5)
Rhinitis	20 (24.7)	25 (29.1)	45 (26.9)
Headache	24 (29.6)	19 (22.1)	43 (25.7)
Pain	16 (19.8)	14 (16.3)	30 (18.0)
Cough increased	14 (17.3)	15 (17.4)	29 (17.4)
Infection	11 (13.6)	18 (20.9)	29 (17.4)
Nausea	5 (6.2)	13 (15.1)	18 (10.8)
Accidental injury	7 (8.6)	10 (11.6)	17 (10.2)
Surgical procedure	5 (6.2)	12 (14.0)	17 (10.2)
Fever	5 (6.2)	10 (11.6)	15 (9.0)
Abdominal pain	6 (7.4)	7 (8.1)	13 (7.8)
Asthenia	6 (7.4)	7 (8.1)	13 (7.8)
Bronchitis	6 (7.4)	6 (7.0)	12 (7.2)
Diarrhea	7 (8.6)	5 (5.8)	12 (7.2)
Dysmenorrhea	5 (6.2)	6 (7.0)	11 (6.6)
Myalgia	6 (7.4)	5 (5.8)	11 (6.6)
Urinary tract infection	5 (6.2)	4 (4.7)	9 (5.4)

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=714)	Regular human insulin (n=709)	Total (n=1423)
Headache	63 (11.6)	66 (9.3)	149 (10.5)
Pain	77 (10.8)	71 (10.0)	148 (10.4)
Infection	72 (10.1)	54 (7.6)	126 (8.9)
Pharyngitis	47 (6.6)	58 (8.2)	105 (7.4)
Rhinitis	58 (8.1)	47 (6.6)	105 (7.4)
Flu syndrome	44 (6.2)	58 (8.2)	102 (7.2)
Surgical procedure	53 (7.4)	48 (6.8)	101 (7.1)

Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Lipodystrophy

Long-term use of insulin, including HUMALOG, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy *[see Dosage and Administration]*.

Weight gain

Weight gain can occur with insulin therapy, including HUMALOG, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Peripheral Edema

Insulin, including HUMALOG, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII)

In a 12-week, randomized, crossover study in adult patients with type 1 diabetes (n=39), the rates of catheter occlusions and infusion site reactions were similar for HUMALOG and regular human insulin treated patients (*see* Table 3).

Table 3: Catheter Occlusions and Infusion Site Reactions

	HUMALOG (n=38)	Regular human insulin (n=39)
Catheter occlusions/ month	0.09	0.10
Infusion site reactions	2.6% (1/38)	2.6% (1/39)

In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

Allergic Reactions

Local Allergy—As with any insulin therapy, patients taking HUMALOG may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of HUMALOG. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including HUMALOG. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular human insulin (n=2969) and 30 patients receiving HUMALOG (n=2944).

Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in HUMALOG *[see Contraindications]*.

Antibody Production

In large clinical trials with patients with type 1 (n=509) and type 2 (n=262) diabetes mellitus, anti-insulin antibody (insulin lispro-specific antibodies, insulin-specific antibodies, cross-reactive antibodies) formation was evaluated in patients receiving both regular human insulin and HUMALOG (including patients previously treated with human insulin and naive patients). As expected, the largest increase in the antibody levels occurred in patients new to insulin therapy. The antibody levels peaked by 12 months and declined over the remaining years of the study. These antibodies do not appear to cause deterioration in glycemic control or necessitate an increase in insulin dose. There was no statistically significant relationship between the change in the total daily insulin dose and the change in percent antibody binding for any of the antibody types.

Postmarketing Experience—The following additional adverse reactions have been identified during post-approval use of HUMALOG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors in which other insulins have been accidentally substituted for HUMALOG have been identified during postapproval use.

DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. Following are some of the examples:

- **Drugs That May Increase the Blood-Glucose-Lowering Effect of HUMALOG and Susceptibility to Hypoglycemia:** Oral antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, pramlintide, disopyramide, fibrates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide).
- **Drugs That May Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones.
- **Drugs That May Increase or Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- **Drugs That May Reduce the Signs of Hypoglycemia:** beta-blockers, clonidine, guanethidine, and reserpine.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMALOG.

Although there are limited clinical studies of the use of HUMALOG in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

Nursing Mothers—It is unknown whether insulin lispro is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HUMALOG is administered to a nursing woman. Use of HUMALOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Pediatric Use—HUMALOG is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. HUMALOG has not been studied in pediatric patients younger than 3 years of age. HUMALOG has not been studied in pediatric patients with type 2 diabetes.

As in adults, the dosage of HUMALOG must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

Geriatric Use—Of the total number of subjects (n=2834) in eight clinical studies of HUMALOG, twelve percent (n=338) were 65 years of age or over. The majority of these had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of HUMALOG action have not been performed.

OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE AND ADMINISTRATION

Dosage Considerations—When given subcutaneously, HUMALOG has a more rapid onset of action and a shorter duration of action than regular human insulin.

The dosage of HUMALOG must be individualized. Blood glucose monitoring is essential in all patients receiving insulin therapy.

The total daily insulin requirement may vary and is usually between 0.5 to 1 unit/kg/day. Insulin requirements may be altered during stress, major illness, or with changes in exercise, meal patterns, or coadministered drugs.

Subcutaneous Administration—HUMALOG should be given within 15 minutes before a meal or immediately after a meal.

HUMALOG given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.

HUMALOG administered by subcutaneous injection should be given in the abdominal wall, thigh, upper arm, or buttocks. Injection sites should be rotated within the same region (abdomen, thigh, upper arm, or buttocks) from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions]*.

Continuous Subcutaneous Infusion (Insulin Pump)—HUMALOG may be administered by continuous subcutaneous infusion by an external insulin pump. Do not use diluted or mixed insulins in external insulin pumps. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy *[see Adverse Reactions]*. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant variability among patients, approximately 50% of the total dose is usually given as meal-related boluses of HUMALOG and the remainder is given as a basal infusion. HUMALOG is recommended for use in pump systems suitable for insulin infusion such as MiniMed, Disetronic, and other equivalent pumps.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HUMALOG 100 units per mL (U-100) is available as:

10 mL vials	NDC 0002-7510-01 (VL-7510)
3 mL vials	NDC 0002-7510-17 (VL-7533)
5 x 3 mL cartridges[1]	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled pen	NDC 0002-8725-59 (HP-8725)
5 x 3 mL Humalog KwikPen (prefilled)	NDC 0002-8799-59 (HP-8799)

Storage

Do not use after the expiration date.

Unopened HUMALOG should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use HUMALOG if it has been frozen. In-use HUMALOG vials, cartridges, pens, and HUMALOG KwikPen® should be stored at room temperature, below 86°F (30°C) and must be used within 28 days or be discarded, even if they still contain HUMALOG. Protect from direct heat and light. See table below:

	Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, (Below 86°F [30°C])
10 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL cartridge	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL prefilled pen	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, **Do not refrigerate.**

Use in an External Insulin Pump—Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days or after exposure to temperatures that exceed 98.6°F (37°C). A HUMALOG 3 mL cartridge used in the D-Tron® pumps should be discarded after 7 days, even if it still contains HUMALOG. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days.

Diluted HUMALOG for Subcutaneous Injection—Diluted HUMALOG may remain in patient use for 28 days when stored at 41°F (5°C) and for 14 days when stored at 86°F (30°C). Do not dilute HUMALOG contained in a cartridge or HUMALOG used in an external insulin pump.

Preparation and Handling

Diluted HUMALOG for Subcutaneous Injection—HUMALOG may be diluted with Sterile Diluent for HUMALOG for subcutaneous injection. Diluting one part HUMALOG to nine parts diluent will yield a concentration one-tenth that of HUMALOG (equivalent to U-10). Diluting one part HUMALOG to one part diluent will yield a concentration one-half that of HUMALOG (equivalent to U-50).

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling and Patient Counseling Information section of the Full Prescribing Information.

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[1] 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® Memoir™ and HumaPen® Luxura™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3-mL insulin delivery device and Disetronic D-TRON® and D-TRON® Plus pumps.

Autopen® is a registered trademark of Owen Mumford, Ltd.

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Additional information can be found at www.humalog.com.

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The True Value of Branded Products

A closer look at ophthalmic generics

With more and more generic ophthalmic medications being introduced, it may be time to take a closer look at these agents and their relationship to their branded counterparts. At first glance, switching from a branded drug to a generic makes sense, especially in the current economic climate. However, in reality, price differentials between branded and generics may or may not be significant.[1] Furthermore, differences in the formulations of generic ophthalmics and their reference drugs suggest that there may be issues other than cost to consider when making treatment decisions.[2]

Branded ophthalmics provide proven and predictable efficacy and safety profiles. The trial samples, patient education, prescription assistance programs, and representative support of branded products contribute to their added value.

Generic drugs may differ from their branded counterparts

Despite FDA requirements that pharmaceutical equivalence and bioequivalence be established, the fact remains that generic products can differ significantly from the reference drugs and sometimes even amongst themselves.[3] Generic bioequivalence is based upon bioavailability, and requires a comparable rate and extent of absorption to its branded counterpart.[4] Unlike systemic drugs where bioavailability may be easily determined by a blood sample, it's difficult to test bioavailability in the eye.[2] As such, the lack of therapeutic bioequivalence testing for ophthalmic generics is a potential concern.[2]

While both branded and generic drugs are reviewed for labeling, chemistry, manufacturing, and quality control, their inactive ingredients, such as preservatives, pH adjusters, thickening agents, and buffers, may differ.[2] These differences, and differences in the manufacturing process itself, can alter the agents' pharmacokinetic properties, including drug dissolution, absorption, and metabolism.[3]

The impact of changing medications

As we know, tolerability, patient comfort, and compliance can be affected by any change in medication.[2] Adjusting a patient's medication regimen while maintaining the balance of efficacy, safety, and tolerability is a constant challenge. The management of chronic ophthalmic conditions, such as glaucoma, is often complex and places significant demands on both physicians and patients. When a patient with glaucoma is stable on current therapy, switching medications—whether it is switching from one branded medication to another or switching from a branded drug to a generic—could potentially have a significant effect on the patient.[2] Even the most superficial differences in generic drug size, color, and packaging may prove problematic for certain patient subpopulations.[5] Therefore, we must do all we can to help.

The consistent value of branded drugs

Branded drugs have the advantage of proven efficacy and safety profiles that have been thoroughly demonstrated in clinical trials and through extensive clinical experience. Consistent performance and predictability are the hallmarks of branded ophthalmics. In the unpredictable world of treating chronic ophthalmic conditions, perhaps the true value of branded drugs is their consistent manufacturing.

In the unpredictable world of treating chronic ophthalmic conditions, perhaps the true value of branded drugs is their consistent manufacturing.

Many ophthalmic drugs are widely covered by managed care organizations, and many manufacturers go to great lengths to keep co-pays to a minimum. Therefore, branded drugs may be affordable in many cases.

Evaluate every substitution

The proven, predictable safety and efficacy profiles of branded drugs that have been established through phase 3 randomized, controlled, multicenter clinical trials and extensive clinical experience are irreplaceable. You may find that branded ophthalmic medications provide efficacy with consistency. Until new testing of generics against their parent drugs for efficacy, safety, and patient comfort is required, weigh the pros and cons of prescribing generics on a case-by-case basis.[2]

The lack of therapeutic bioequivalence testing for ophthalmic generics is a potential concern.

Differences in the FDA-Approval Process for Generic and Branded Ophthalmics

FDA Approval: Areas Evaluated	Generic	Branded
Animal Studies Preclinical data to establish efficacy and safety[4]		✓
Clinical Studies Clinical data to establish efficacy and safety[4]		✓
Bioavailability Evaluation of rate and extent of absorption[4]		✓
Bioequivalence Comparable rate and extent of absorption[4]	✓ (Note: Difficult to establish bioequivalence in the eye.)[2]	

1. Mager DE, Cox ER. Relationship between generic and preferred-brand prescription copayment differentials and generic fill rate. *Am J Manag Care.* 2007;13(6, pt 2):347-352. **2.** Cantor LB. Ophthalmic generic drug approval process: implications for efficacy and safety. *J Glaucoma.* 1997;6(5):344-349. **3.** Genazzani AA, Pattarino F. Difficulties in the production of identical drug products from a pharmaceutical technology viewpoint. *Drugs R D.* 2008;9(2):65-72. **4.** US Food and Drug Administration. Abbreviated New Drug Application (ANDA): Generics. US Food and Drug Administration Web site. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm. Updated December 4, 2009. Accessed December 7, 2009. **5.** Meredith P. Bioequivalence and other unresolved issues in generic drug substitution. *Clin Ther.* 2003;25(11):2875-2890.

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