

CARLOS JORGE DA SILVA

**NEUROTOXICIDADE POR MANGANÊS E HEMODIÁLISE:
UM ESTUDO CLÍNICO, LABORATORIAL E DE
RESSONÂNCIA MAGNÉTICA**

Tese apresentada ao Curso de Pós-Graduação da Faculdade de Ciências Médicas da Santa Casa de São Paulo para obtenção do título de Doutor em Medicina.

São Paulo

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Área de Concentração:
Ciências da Saúde

Orientador:
Prof. Dr. Antônio José da Rocha

Coorientadores:
Prof. Dr. Luiz Antonio Miorin
Profa. Dra. Maria Fernanda Mendes

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Maria Fernanda Mendes

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pelo amor, cumplicidade e companheirismo inesgotáveis.*

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"Toda convicção é um cárcere."

(Friedrich Nietzsche)

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Aos pacientes renais crônicos, razão maior deste projeto.

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INTRODUÇÃO

Pacientes em uso de nutrição parenteral e aqueles com encefalopatia portossistêmica secundária à doença hepática crônica e a *shunts* venosos portossistêmicos congênitos ou adquiridos frequentemente apresentam acúmulo de manganês (Mn) na adeno-hipófise e em regiões específicas do encéfalo, mais precisamente nos globos pálidos, putâmens, regiões subtalâmicas, substâncias negras e algumas vezes difusamente na substância branca dos hemisférios cerebrais (Raskin et al, 1964; Inoue et al, 1991; Krieger et al, 1997; Maeda et al, 1997; Dietemann et al, 1998; Akahoshi et al, 2000; da Rocha et al, 2004).

O marcador biológico do acúmulo cerebral de Mn é o hipersinal bilateral e simétrico nos núcleos da base, notadamente nos globos pálidos, evidenciado nas sequências ponderadas em T1 de ressonância magnética (RM) (Inoue et al, 1991; Nelson et al, 1993; Maeda et al, 1997; Dietemann et al, 1998; da Rocha et al, 2004; Josephs et al, 2005; Dorman et al, 2006; Kenangil et al, 2006; Uchino et al, 2007; da Silva et al, 2008). Alguns autores descreveram o mesmo padrão de acúmulo de Mn em soldadores, secundário à inalação de vapores de solda ricos neste elemento químico (Josephs et al, 2005; Kenangil et al, 2006; da Silva et al, 2008). O manganismo apresenta-se comumente como uma síndrome parkinsoniana (Nelson et al, 1993; da Rocha et al, 2004; Josephs et al, 2005; Kenangil et al, 2006; da Silva et al, 2008). Entretanto, uma síndrome mioclônica multifocal com distúrbio cognitivo discreto, uma síndrome mista com sintomas vestibulares e auditivos, bem como uma síndrome menor caracterizada por déficit cognitivo subjetivo, ansiedade e apnéia do sono também têm sido descritas (Josephs et al, 2005; da Silva et al, 2008).

Na prática da neurorradiologia na Santa Casa de São Paulo, observamos também a ocorrência de um padrão idêntico de RM em indivíduos renais crônicos submetidos à hemodiálise, mesmo na ausência dos outros fatores de risco acima mencionados. Não está confirmada a razão da ocorrência desse padrão de imagem nesse grupo de indivíduos. Admitimos que ele também reflita o acúmulo de Mn, secundário ao procedimento dialítico. Após pesquisa na base de dados Medline® chamou-nos a atenção a inexistência, naquela época, de uma descrição na literatura de língua inglesa dessa associação. Propusemo-nos a estudar as bases desse

fenômeno e, para tanto, desenvolvemos um projeto científico visando entender os padrões clínicos e de RM comparados à dosagem sérica do Mn, em pacientes com insuficiência renal crônica, dialíticos e não dialíticos confrontados com aqueles de um grupo controle saudável. Esse estudo abrangerá também o melhor entendimento evolutivo dessa nova associação, com a possível reversão após a interrupção do tratamento dialítico devido a instituição de medidas efetivas para o restabelecimento da função renal com o transplante de rim.

OBJETIVOS

Objetivos primários

Avaliar o sinal palidal nas sequências ponderadas em T1 e realizar a busca ativa de sintomas neurológicos relacionados ao manganismo em indivíduos saudáveis e naqueles com insuficiência renal crônica.

Buscar a correlação dos níveis séricos de Mn nesta série de pacientes

Objetivo secundário

Análise prospectiva do sinal palidal e sua correlação com os níveis séricos de Mn no indivíduo submetido a transplante de rim, com restituição da função renal.

CASUÍSTICA E MÉTODO

Os pacientes renais crônicos foram subdivididos em dialíticos (grupo 1) e não dialíticos (grupo 2), todos provenientes do Serviço de Nefrologia do Departamento de Medicina da Santa Casa de Misericórdia de São Paulo. Os indivíduos saudáveis (grupo 3) são provenientes do Serviço de Diagnóstico por Imagem da Santa Casa. O protocolo foi aprovado pela Comissão de Ética da Instituição (Anexo 1) e todos assinaram o Termo de Consentimento Livre e Esclarecido (Anexo 2).

Todos foram submetidos a exames de RM sem contraste com as seguintes sequências: T1 SE (TR 509 ms, TE 14 ms), FLAIR (TR 11000 ms, TE 140 ms, TI 2600 ms) e T2 FFE (TR 619 ms, TE 21 ms, *flip angle* 15 graus) em um equipamento de 1,0 T. Todos foram submetidos ao exame neurológico e à dosagem sérica de Mn

por espectrofotometria de absorção atômica com forno de grafite (Fleury Medicina e Saúde).

Os indivíduos dos grupos 1 e 2 foram submetidos a exames laboratoriais de função hepática, incluindo sorologia para hepatites A, vírus B e C, HIV, hemograma, dosagens de eletrólitos, dosagens de ferro, transferrina e ferritina, perfil tireoidiano e paratireoidiano, testes de função renal.

Aqueles do grupo 1 foram submetidos a estudo ultrassonográfico com Doppler do abdome superior, para a avaliação hepática e do sistema porta, bem como à tomografia computadorizada (TC) do crânio sem contraste.

A unidade de hemodiálise da Instituição está em conformidade com as normas do Ministério da Saúde para funcionamento regular.

Critérios de inclusão

Indivíduos que concordaram em participar do protocolo.

Para aqueles dos grupos 1 e 2, níveis de creatinina acima de 1,5 mg/dL e *clearance* de creatinina abaixo de 60 mL/min. Para os do grupo 1, no mínimo 2 anos de hemodiálise.

Critérios de exclusão

Indivíduos com contra-indicação para RM, indivíduos com sinais de insuficiência hepática, com sorologia positiva para vírus da hepatite B, C ou retrovírose, evidência de shunts porto-sistêmicos congênitos ou adquiridos demonstrados por exame de ultrassom Doppler, pacientes com obstrução de vias biliares ao exame ultrassonográfico, presença de calcificações palidais exuberantes na TC ou evidência de depósito palidal de material ferromagnético na RM.

Indivíduos em nutrição parenteral total, soldadores e aqueles com história de abuso de álcool também foram excluídos.

Cronograma

Na casuística do primeiro artigo (janeiro-maio de 2006), foram incluídos 5 pacientes no grupo 1 e 4 pacientes no grupo 2.

Na casuística do segundo artigo (janeiro/2006-junho/2009) foram incluídos 48 pacientes, sendo 16 em cada um dos 3 grupos.

Em novembro de 2007, uma paciente sem sintomas neurológicos do grupo 1 foi submetida a transplante de rim, com restabelecimento da função renal. Foi instituída a avaliação prospectiva com a realização de estudos de RM de 4 em 4 meses e correlação simultânea quanto aos níveis séricos de Mn. O tempo de avaliação foi de 1 ano, com término em outubro de 2008.

Análise dos achados clínicos, de imagem e das dosagens séricas de Mn

Os exames de RM foram analisados por um neurorradiologista (AJR), que desconhecia os resultados da avaliação neurológica e da dosagem sérica de Mn. As dosagens de Mn sérico foram realizadas sem o conhecimento dos resultados da avaliação neurológica e de RM. Os pacientes foram examinados por uma neurologista (MFM) que desconhecia os resultados da RM e das dosagens séricas de Mn.

Análise estatística

Comparamos o gênero, a idade, os achados clínicos, os níveis séricos de Mn e os achados de RM do grupo 1, com aqueles dos grupos 2 e 3 isoladamente e de forma combinada (grupos 2 + 3).

Avaliamos a possível associação entre manganismo e baixos níveis séricos de hemoglobina, ferritina e ferro, bem como com baixa saturação de transferrina.

Descrevemos os dados qualitativos em frequências simples e relativas (porcentagens), bem como os dados quantitativos em médias e desvios-padrão.

Os dados laboratoriais foram analisados de forma quantitativa (valores originais) e qualitativa (classificação em normal ou alterado). Os dados clínicos e de RM foram analisados de forma qualitativa (normal ou alterado).

Utilizamos modelos de análise de variância (ANOVA) para a comparação de variáveis quantitativas entre os 3 grupos. Usamos o teste qui-quadrado de Pearson ou o teste exato de Fisher para a comparação de variáveis qualitativas entre os 3 grupos. Adotamos o intervalo de confiança de 95% para as médias e o nível de significância de foi de 0,05. Utilizamos o programa estatístico SPSS para o Windows, versão 17.0 para efetuar os cálculos.

RESULTADOS

Artigo 1 - A preliminary study revealing a new association in patients undergoing maintenance hemodialysis: manganese symptoms and T1 hyperintense changes in the basal ganglia.

A RM demonstrou áreas simétricas de hipersinal nos globos pálidos, detectadas pelas seqüências ponderadas em T1 nos 5 pacientes renais crônicos em hemodiálise estudados, todos com níveis séricos elevados, sendo que 4 deles exibiram sintomas atribuíveis à neurotoxicidade pelo Mn. Nenhum dos quatro pacientes renais crônicos sem tratamento dialítico, selecionados para comparação, exibiu anormalidades clínicas ou de imagem.

Artigo 2 - Manganese neurotoxicity in patients undergoing maintenance hemodialysis: a clinical, laboratory, and magnetic resonance imaging study.

A RM demonstrou áreas simétricas de hipersinal nos globos pálidos, detectadas pelas seqüências ponderadas em T1 em todos os pacientes do grupo 1 ($p < 0,001$). Todos os pacientes do grupo 1 apresentaram níveis séricos elevados de Mn ($p < 0,001$) e metade deles exibiu sintomas atribuíveis à neurotoxicidade pelo Mn ($p < 0,001$). Nenhum dos pacientes dos grupos 2 e 3 exibiu alterações de imagem ou sintomas atribuíveis ao acúmulo de Mn, apesar de 4 (25%) pacientes do grupo 2 e 8

(50%) pacientes do grupo 3 apresentarem elevados níveis séricos deste elemento. Não houve diferença estatisticamente significativa entre indivíduos anêmicos e não anêmicos quanto à ocorrência de manganismo.

Foi confirmado o desaparecimento progressivo do hipersinal palidal seletivo em T1 daquela paciente transplantada. A análise visual demonstrou a normalização progressiva da intensidade de sinal ao longo do período de avaliação (1 ano), bem como a normalização progressiva nos níveis de Mn sérico.

DISCUSSÃO

O hipersinal palidal em T1 reflete o acúmulo de Mn

Nossos achados corroboram a afirmativa prévia de que o hipersinal palidal em T1 é um marcador biológico do acúmulo de Mn no encéfalo (Inoue et al, 1991; Nelson et al, 1993; Maeda et al, 1997; Dietemann et al, 1998; da Rocha et al, 2004; Josephs et al, 2005; Dorman et al, 2006; Kenangil et al, 2006; Uchino et al, 2007; da Silva et al, 2008). Contudo, deve ser ressaltado que a presença de hipersinal palidal em T1 não é um achado específico, podendo ser encontrado em outras condições como: hiperglicemia não cetótica, hipóxia, neurofibromatose tipo I, doença de Wilson, kernicterus agudo, hemorragias e depósitos de cálcio (Dell et al, 1988; Terada et al, 1996; Mochizuki et al, 1997; Lee et al, 2002; Govaert et al, 2003; Nakajo et al, 2003; Dorman et al, 2006).

Os depósitos de cálcio podem ocorrer em nefropatas crônicos secundários à hiperfunção das paratireóides. Porém, a análise dos estudos de TC e das sequências T2 FFE não demonstraram depósitos proeminentes de cálcio nos globos pálidos, que pudessem ser correlacionados à extensão das áreas encontradas de hipersinal palidal em T1 nos pacientes do grupo 1. Acreditamos que este conjunto de argumentos favoreça a possibilidade de que o Mn seja o responsável pelo hipersinal palidal em T1.

A hemodiálise é o principal fator de risco para o manganismo

Dados de roedores sugerem que a anemia e a deficiência de ferro podem ser fatores de risco para o manganismo (Fitsanakis et al, 2009). Nosso estudo não mostrou correlação positiva desta associação de fatores. Entretanto, o poder do teste foi de apenas 31% (desejado = acima de 80%). Portanto, o único fator que diferencia o grupo 1 dos demais quanto aos achados clínicos, laboratoriais e de imagem é a hemodiálise. Acreditamos que a hemodiálise seja, no mínimo, o principal fator de risco para a ocorrência do manganismo em nossos pacientes.

Descrições de acúmulo de Mn sérico e encefálico em pacientes dialíticos

Recentemente, um grupo de autores (Ohtake et al, 2005) descreveu sintomas parkinsonianos em um paciente com nefropatia diabética em tratamento dialítico crônico. O acúmulo foi atribuído a um suplemento vitamínico rico em Mn (extrato de *Chlorella*). Entretanto, o padrão de imagem publicado não corresponde aos achados clássicos de acúmulo de Mn que, acreditamos, deva decorrer da síndrome do desequilíbrio da diálise.

Nós descrevemos, pela primeira vez, o acúmulo de Mn sérico e encefálico em indivíduos submetidos à hemodiálise, sem uma causa dietética identificável (da Silva et al, 2007).

Fisiopatologia do acúmulo de Mn sérico e encefálico no grupo 1

Para o desenvolvimento da discussão relativa à fisiopatologia do acúmulo de Mn sérico e encefálico serão avaliadas as seguintes hipóteses:

- 1- Distúrbio da excreção do Mn pelo sistema biliar.
- 2- O efeito da uremia no metabolismo do Mn.
- 3- Mn originário do dialisado.
- 4- Ingestão excessiva de Mn que ultrapassa a capacidade excretória.
- 5- Alteração da capacidade de ligação transferrina-Mn na hemodiálise.

Distúrbio da excreção do Mn pelo sistema biliar

O Mn circula no sangue como Mn^{+++} (ligado à transferrina), como Mn^{++} ligado à alfa-2 macroglobulina, sendo este complexo fraco, onde o Mn se dissocia e é excretado pelo fígado, ou como Mn^{++} na forma de íon livre (Davidsson et al, 1989a). A maior rota de excreção do Mn ocorre pelo sistema biliar (Scheuhammer, Cherian, 1982). Nenhum dos pacientes do grupo 1 apresentou disfunção hepática ou obstrução do sistema biliar, de acordo com os dados laboratoriais e de ultrassonografia abdominal, respectivamente. Por essa avaliação, esta hipótese não nos parece plausível.

O efeito da uremia no metabolismo do Mn

A excreção urinária do Mn é insignificante, sendo que a anúria decorrente da insuficiência renal crônica não influencia o metabolismo do Mn (Papavasiliou et al, 1966). Portanto, esta não é uma hipótese plausível.

Mn originário do dialisado

É fato que a contaminação do dialisado por Mn poderia determinar toxicidade por este elemento (Taylor, Price, 1982). Contudo, o dialisado utilizado está em conformidade com as normas do Ministério da Saúde e, para tanto, não contém Mn detectável. Esta hipótese também não se mostra plausível.

Ingestão excessiva de Mn que ultrapassa a capacidade excretória

Todos os pacientes do grupo 1 ($p < 0,001$) apresentaram altos níveis séricos de Mn. Apesar de 4 (25%) pacientes do grupo 2 e 8 (50%) indivíduos do grupo 3 exibirem altos níveis séricos de Mn, todos eram assintomáticos e nenhum apresentou o hipersinal palidal bilateral em T1. O Mn é proveniente da dieta. A análise dos dados disponíveis permite considerar esta hipótese mais plausível que as anteriores, apesar de nenhum dos indivíduos ter recebido uma dieta ou mesmo suplementos orais ricos em Mn. Apesar disso, a dieta pode explicar a origem, mas não o acúmulo de Mn no encéfalo.

Alteração da capacidade de ligação transferrina-Mn na hemodiálise

O Mn sérico dosado corresponde ao Mn ligado à transferrina. Se há saturação da transferrina, o Mn sérico resultará aumentado. O Mn livre excedente que não consegue se ligar à transferrina já saturada será excretado pelo fígado ou se acumulará nos tecidos, mas não no sangue (Davidsson et al, 1989b; Wang et al, 1997). Ou seja, o alto nível sérico de Mn não se correlaciona com a intensidade de exposição e sim com o nível de saturação da transferrina (Josephs et al, 2005).

Por que então os pacientes do grupo 1 teriam transferrina significativamente mais saturada que os demais e qual a correlação disto com o acúmulo deste elemento no encéfalo?

Gidden e colaboradores (Gidden et al, 1980) demonstraram que a capacidade de ligação da transferrina com o Mn no soro de indivíduos em hemodiálise é bastante reduzida, quando comparada ao soro de controles normais. Conseqüentemente haverá uma maior concentração de Mn livre no sangue (não mensurado), que passaria a se acumular nos tecidos. Supomos que esse aumento do Mn livre seja maior que a capacidade excretória do fígado. Talvez esta seja a hipótese mais provável para o acúmulo de Mn nos tecidos.

Nossos achados corroboram os de Schabowski e colaboradores (Schabowski et al, 1994), que em um estudo *postmortem*, demonstraram aumento das concentrações de Mn em tecidos de pacientes submetidos à hemodiálise crônica. A concentração de Mn no encéfalo chega a ser 100 vezes maior que a do plasma (Keen et al, 1984), sugerindo um transporte ativo ou um carreador seletivo deste elemento. Supomos que ao atingir um equilíbrio dinâmico com os tecidos, a concentração sérica de Mn livre aumente ainda mais, aumentando com isto a saturação da transferrina, mesmo que ela tenha uma menor capacidade de ligação com este elemento. O Mn finalmente passa a ser dosado e sua concentração passa a ser registrada como “elevada” nos exames de sangue. Acreditamos que sejam necessários alguns anos de hemodiálise para que tais fenômenos ocorram.

Predileção do Mn pelos globos pálidos

Mecanismo da neurotoxicidade pelo Mn

Os núcleos da base e, principalmente, os globos pálidos possuem um grande número de receptores de transferrina (Heilbronn, Eriksson, 1997). Dentro do neurônio, o Mn^{++} é rapidamente sequestrado na mitocôndria, onde promove o acúmulo de Ca^{++} mitocondrial através da inibição das bombas de exportação de Ca^{++} dependentes e independentes de Na^+ (Gavin et al, 1999). O Mn^{++} também inibe a F1-ATPase mitocondrial com consequente depleção de ATP (Gavin et al, 1992).

Além disso, nos núcleos da base, apenas os globos pálidos recebem seletivamente aferentes glutaminérgicos dos núcleos subtalâmicos (Rouse et al, 2000). O glutamato é um neurotransmissor excitatório que exacerba os efeitos do Mn, pois ambos têm mecanismos de toxicidade semelhantes (Broulliet et al, 1993). O glutamato determina neurotoxicidade por acúmulo intracelular de Ca^{++} , que se inicia na ligação do glutamato em seu receptor ionotrópico na membrana celular. Este receptor ionotrópico permite a entrada de Ca^{++} ou de Mn^{++} no neurônio (Kannurpatti et al, 2000). Dentro do neurônio, o Ca^{++} , assim como o Mn^{++} , também é rapidamente sequestrado na mitocôndria pela bomba de Ca^{++} , provocando mudanças da permeabilidade da membrana mitocondrial e disparando sinais de toxicidade intracelular (Luo et al, 1997).

Em última análise, a neurotoxicidade induzida pelo Mn é mediada pelo colapso mitocondrial que inicia a apoptose e necrose celular pela formação de compostos altamente oxidantes (Roth, Garrick, 2003).

Variação na vulnerabilidade ao manganismo

Apenas metade dos pacientes em hemodiálise (n=8) apresentou sintomas de manganismo. Além disso, um paciente com apenas 3 anos de hemodiálise apresentou síndrome parkinsoniana e outro com 7 anos de hemodiálise era assintomático, denotando uma variação na vulnerabilidade ao manganismo.

A principal proteína transportadora de Mn para o interior das células é o DMT1 (transportador de metal divalente) (Roth, Garrick, 2003). O gene do DMT1 produz 4 isoformas deste transportador (Gunshin et al, 1997), que variam quanto à distribuição e concentração nas organelas e nas vesículas endossomais, bem como quanto aos mecanismos de regulação (Tabuchi et al, 2002). O DMT1 é tido como o principal fator limitante para a neurotoxicidade induzida pelo Mn (Roth, 2009). Estes argumentos podem explicar a variação na vulnerabilidade dos pacientes do grupo 1 a desenvolverem manganismo.

Os mecanismos do acúmulo de Mn no encéfalo ainda não estão completamente esclarecidos. Possivelmente este acúmulo decorra do influxo de Mn livre oriundo do sangue, devido às alterações na capacidade de ligação deste elemento com a transferrina nos pacientes em hemodiálise, iniciando a disfunção dos sistemas de transporte do Mn no encéfalo. Retirado o fator de risco (hemodiálise crônica), o hipersinal palidal bilateral em T1 e os altos níveis séricos de Mn tendem a desaparecer, como demonstrado na paciente submetida ao transplante de rim com restabelecimento da função renal.

Os objetivos da hemodiálise são garantir aos pacientes uma nutrição adequada, manter o equilíbrio hidroeletrolítico, corrigir deficiências hormonais, minimizar as hospitalizações, prolongar e aumentar a qualidade de vida. Sem o tratamento dialítico, inúmeros pacientes renais crônicos teriam falecido prematuramente (Ifudu, 1998).

Entretanto, o estudo desta nova associação entre hemodiálise crônica e a deposição de Mn no encéfalo nos permitiu alcançar as bases do entendimento dos mecanismos deste acúmulo. O desenvolvimento de tal projeto nos garantiu a descrição original, do relato preliminar, desta nova associação (da Silva et al, 2007). Prossequimos o desenvolvimento do estudo com melhor entendimento das diferentes combinações de achados clínicos, laboratoriais e de imagem, como descrito acima, à medida que a casuística aumentava nos dois anos seguintes. O cumprimento dos objetivos relativos ao desenvolvimento do projeto desta tese pôde ainda ser ampliado, com o desenvolvimento de outro estudo, em curso, e que poderá no futuro garantir outras publicações. O alargamento dos horizontes

científicos desta linha de pesquisa nos permitiu incluir no escopo desta tese a premente necessidade do entendimento desse fenômeno nos indivíduos submetidos ao transplante renal. Este segundo projeto deverá ser objeto de um novo desenvolvimento, mas já nos habilita a apresentar o relato de um caso índice com acompanhamento seriado pré e pós-transplante renal. O desenvolvimento do projeto subsequente ainda demandará mais tempo de acompanhamento, além do previsto no cronograma firmado para o propósito corrente.

Desta forma, acredito ter contribuído para a ampliação das fronteiras do conhecimento científico relativo à ocorrência de manganismo em indivíduos renais crônicos submetidos à hemodiálise. Nós produzimos dois artigos originais, sendo um publicado e o outro submetido a periódicos internacionais indexados (Medline[®]), com seletiva política editorial.

O primeiro artigo: ***“A preliminary study revealing a new association in patients undergoing maintenance hemodialysis: manganism symptoms and T1 hyperintense changes in the basal ganglia”*** foi publicado no periódico *American Journal of Neuroradiology* em 2007.

O segundo artigo: ***“Manganese neurotoxicity in patients undergoing maintenance hemodialysis: a clinical, laboratory, and magnetic resonance imaging study”*** foi submetido ao periódico *Nephrology Dialysis Transplantation* em 2010.

**ORIGINAL
RESEARCH**

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A Preliminary Study Revealing a New Association in Patients Undergoing Maintenance Hemodialysis: Manganism Symptoms and T1 Hyperintense Changes in the Basal Ganglia

BACKGROUND AND PURPOSE: Patients undergoing parenteral nutrition and those with portosystemic encephalopathy secondary to chronic liver disease and acquired and congenital portosystemic venous shunts frequently present manganese deposition in the basal ganglia, detected by MR imaging as hyperintense areas on T1-weighted sequences. We also observed similar abnormalities in the basal ganglia of patients with chronic renal failure undergoing maintenance hemodialysis. Our aim was to evaluate the pallidal signal intensity on T1-weighted images in a series of patients undergoing hemodialysis, with further evaluation of serum manganese levels and neurologic correlation, comparing them with patients with chronic renal failure without dialytic treatment.

MATERIALS AND METHODS: We performed MR imaging examinations in 9 patients with chronic renal failure, 5 of whom were undergoing hemodialysis. An experienced neuroradiologist scrutinized the presence of symmetric hyperintensities in the basal ganglia on T1-weighted sequences. We also determined the serum manganese levels and performed the neurologic evaluations in all patients.

RESULTS: All patients undergoing hemodialysis presented elevated serum manganese levels and symmetric hyperintensities within the globus pallidus. In this group, 4 patients presented with parkinsonian symptoms, myoclonus, and syndromes with vestibular and vestibular-auditory symptoms. The patients without dialytic treatment presented with neither bilaterally increased T1 MR imaging signal intensity within the globus pallidus nor symptoms of manganism.

CONCLUSION: Our preliminary results demonstrated the occurrence of bilateral pallidal hyperintensity on T1-weighted images in all patients undergoing hemodialysis associated with high serum manganese levels, revealing a new association.

Patients undergoing parenteral nutrition and those with portosystemic encephalopathy secondary to chronic liver disease and acquired and congenital portosystemic venous shunts frequently present manganese accumulation in the adenohypophysis and in specific regions of the brain, more precisely in the globus pallidus, putamen, subthalamic region, substantia nigra, and sometimes diffusely in hemispheric white matter.¹⁻⁷ A biologic marker of manganese accumulation within the central nervous system (CNS) is bilaterally increased T1 MR imaging signal intensity within the basal ganglia, especially in the globus pallidus but also in the striatum.⁸⁻²¹ Recently, some authors have described the same pattern of manganese accumulation in welders, secondary to inhalation of ambient welding fumes with reported inadequate ventilation or other safety measures.^{10,15-17} Although T1 signal-intensity changes in these nuclei may be seen in several different conditions such as nonketotic hyperglycemic episodes, hypoxia, neurofibromatosis, calcium accumulation, Wilson disease, and the early phase of kernicterus, it is an uncommon pattern.²²⁻²⁷ Manganese neurotoxicity presents commonly as a parkinsonian syndrome,^{6,10,11,15-17,28-31} al-

though a syndrome of multifocal myoclonus and limited cognitive impairment, a mixed syndrome with vestibular-auditory symptoms, and a minor syndrome with subjective cognitive impairment, anxiety, and sleep apnea were also described in this setting.¹⁵ We have observed a similar pattern of bilaterally increased T1 MR imaging signal intensity restricted to the globus pallidus of patients with chronic renal failure undergoing hemodialysis. The reason for this phenomenon is, as yet, unclear, and we presume that these signal-intensity abnormalities may also reflect manganese accumulation in the CNS, which should raise important questions concerning the prevention of manganism in this setting.

Our aim was to evaluate the pallidal signal intensity on T1-weighted images, to perform neurologic correlation based on an active search for symptoms related to manganism, and to determine the serum manganese levels of a series of patients undergoing maintenance hemodialysis, comparing these individuals with patients with chronic renal failure without dialytic treatment.

Methods

Our institutional review board approved this study, and we obtained informed consent from all patients. At a minimum, all patients had blood studies (complete blood count; chemistry profile; total serum protein levels; bilirubin levels; hepatitis B, C, and HIV tests; iron studies; and thyroid, parathyroid, liver, and renal function tests). Our hemodialysis unit is in accordance with the laws of The National Sanitary Vigilance Agency.

We performed brain MR imaging at 1T in all patients. After 3

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Table 1: Clinical data and serum manganese levels of the 9 patients with chronic renal failure

Patient	Age (y)	Sex	Mn (ng/mL)	Clinical Features	Hemodialysis
1	48	F	1.18	Parkinsonian symptoms and a mixed syndrome with prominent vestibular auditory symptoms	Yes
2	33	M	0.86	Vestibular syndrome	Yes
3	27	M	0.98	Unremarkable	Yes
4	45	M	2.24	Myoclonus	Yes
5	43	M	1.35	Parkinsonian symptoms	Yes
6	74	F	0.62	Unremarkable	No
7	62	F	0.77	Unremarkable	No
8	22	F	0.99	Unremarkable	No
9	38	M	0.87	Unremarkable	No

Note:—Mn indicates manganese.

Table 2: Serum creatinine, BUN, hemoglobin, hematocrit, albumin, and calcium levels of the 9 patients with chronic renal failure

Patient	Creatinine (mg/dL)	BUN (mg/dL)	Hemoglobin (g/dL)	Hematocrit (%)	Albumin (g/dL)	Calcium (mg/dL)
1	10.6	96.5	12.9	38.2	4.0	8.9
2	14.8	79.0	9.1	27.3	4.4	11.3
3	13.1	95.5	10.9	32.6	4.2	9.7
4	11.2	125.0	7.6	23.0	3.8	11.5
5	18.9	158.0	10.5	32.6	4.0	7.7
6	11.0	58.5	8.5	26.9	3.5	8.7
7	1.9	35.0	9.2	30.2	3.8	11.5
8	1.7	37.0	10.4	32.0	2.4	7.7
9	14.9	71.5	8.4	27.7	2.4	8.5

Note:—BUN indicates blood urea nitrogen.

localizing scans in the axial, coronal, and sagittal planes, axial sections covering the whole brain were aligned with the bicommissural line. Imaging parameters were identical (24-cm FOV, 6-mm thickness, 0.6-mm gap, 205 × 512 matrix). Our protocol included an axial turbo spin-echo (TSE) fluid-attenuated inversion recovery (FLAIR) sequence (TR, 11,000 ms; TE, 140 ms; TI, 2600 ms, TSE factor, 29) and a spin-echo acquisition to obtain T1-weighted images (TR, 509 ms; TE, 14 ms). We also performed an axial T2* sequence (TR, 615 ms; TE, 21 ms; flip angle, 15°) to exclude hemorrhagic lesions in the basal ganglia. For each patient undergoing hemodialysis, we additionally performed an axial nonenhanced brain CT (20-cm FOV, 5-mm infratentorial and 10-mm supratentorial thickness, 512 × 512 matrix) to exclude prominent calcifications in the basal ganglia and an abdominal Doppler ultrasonography to exclude hepatic portosystemic venous shunts.

The inclusion criteria were the following: in patients who agreed to participate in this protocol, serum creatinine level above 1.5 mg/dL and creatinine clearance below 60 mL per minute. We included only individuals who had undergone hemodialysis for more than 2 years. The exclusion criteria were the following: MR imaging contraindication; positive tests for hepatitis B, C, or HIV; hepatic failure; hepatic portosystemic venous shunt or biliary obstruction on abdominal Doppler ultrasonography; elevated serum bilirubin levels; detection of exuberant calcifications or hemorrhage in basal ganglia on CT or MR imaging; total parenteral nutrition; and welding activity.

From January to May 2006, we consecutively enrolled 9 patients (5 men) with chronic renal failure at our institution, 5 of whom were undergoing maintenance hemodialysis. An experienced neuroradiologist (A.J.R.), blinded for clinical data, analyzed the MR images and CT scans of each patient independently. The films were presented in random order (not sequential) without identification. MR imaging and CT studies were not presented together, and he searched for the presence of bilaterally increased T1 MR imaging signal intensity within the basal ganglia, especially in the globus pallidus. We obtained serum manganese levels of all patients by means of atomic absorption spectrophotometry and considered values above 0.85 ng/mL as elevated. An experienced neurologist (M.F.M.), blinded for imaging data, performed neurologic correlation in all patients based on an active search for symptoms related to manganism.

Results

Clinical data, serum manganese levels, and some blood study results are summarized in Tables 1 and 2.

Patients 8 and 9 presented with low albumin levels (normal range, 3.5–5.5 g/dL) due to associated nephrotic syndrome. In the dialytic group, patients 2 and 4 presented with hypercalcemia (normal range, 8.5–10.2 mg/dL), but none of those showed calcifications in the basal ganglia on CT scans. Only 1 individual in this group (patient 1) presented with faint bilateral foci of calcification in the medial aspect of the globus pallidus on CT, also demonstrated as small marked hypointense foci on T2* sequences (Fig 1). All patients undergoing hemodialysis presented with high serum manganese levels and bilateral pallidal hyperintensities on T1-weighted images (Fig 1). None of the patients without dialytic treatment presented with such signal-intensity abnormalities on MR imaging (Fig 2), though 2 of them presented with elevated serum manganese levels. In the nondialytic group, only patient 7 presented with hypercalcemia, and her MR images showed small bilateral foci of marked hypointensity in the medial aspect of the globus pallidus on T2* sequences.

The results of the remaining blood studies (not shown) were unremarkable. None of our patients received oral supplements rich in manganese, and all of them had hydric restriction, hypokalemic and hyposodic diets, and oral supplements of vitamin B and folic acid. Our patients without dialytic treatment also had a hypoproteic diet.

On the basis of the neurologic examination, we recognized 2 different clinical syndromes, parkinsonian symptoms and myoclonus, in 4 of 5 patients undergoing hemodialysis as follows:

Mixed Syndrome with Vestibular-Auditory Symptoms. Patient 1 related left hearing loss, disequilibrium, and tinnitus for more than 5 months, confirmed by neurologic examination. Her brain stem did not show any signal-intensity abnormalities on MR imaging.

Vestibular Syndrome. Patient 2 related disequilibrium for more than 1 year and occasional left-gait deviation, confirmed by neurologic examination. His brain stem did not show any signal-intensity abnormalities on MR imaging.

Parkinsonian Symptom. Tremor was the clinical presentation in patients 1 and 5. In patient 1, tremor was greater in the upper extremities and at the end of movements for more than 5 months. In patient 5, there was only a slight and incessant rest tremor in the upper extremities.

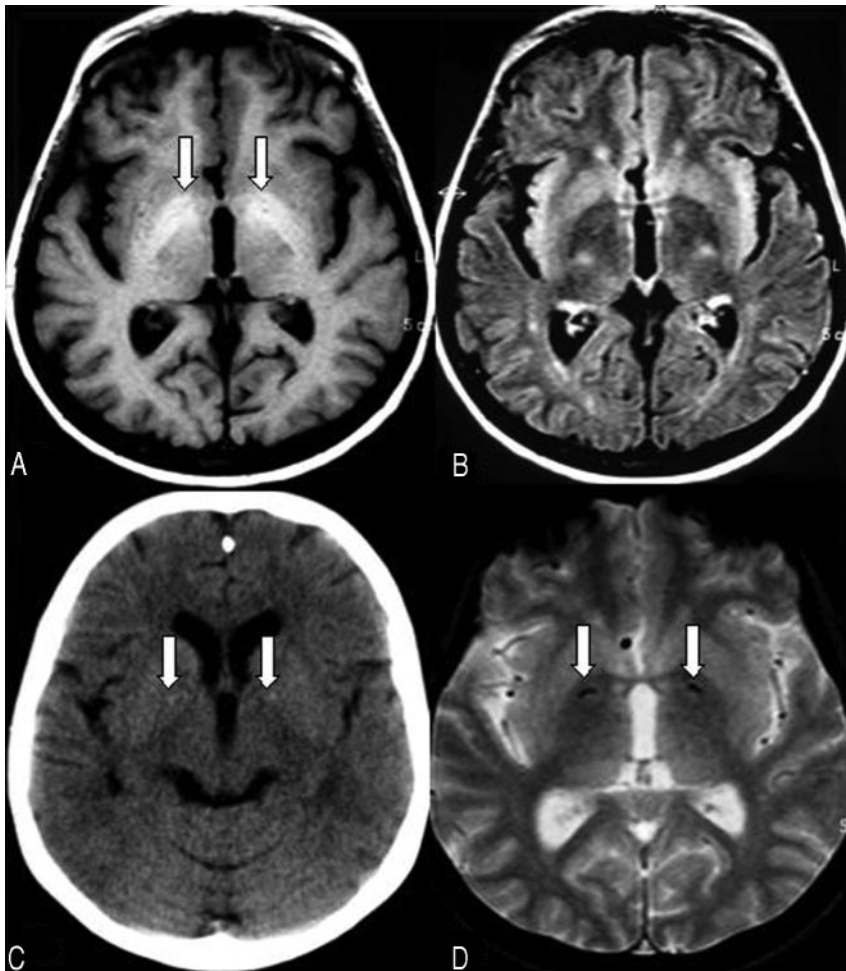


Fig 1. Patient 1. A, Axial T1-weighted image shows bilateral and symmetric hyperintensities within the globus pallidus (arrows). B, Axial FLAIR imaging finding is normal. C, CT image shows faint bilateral foci of calcification in the medial aspect of the globus pallidus (arrows), with precise correspondence on the T2* (D) sequence (arrows).

Recently, Ohtake et al³⁷ described manganese-induced parkinsonism in a man with diabetic nephropathy undergoing maintenance hemodialysis, in whom the cause of manganese accumulation was the intake of an oral supplement (*Chlorella* organism extract) rich in this trace metal. The authors showed MR imaging findings characterized by symmetric basal ganglia hypointensity on T1-weighted and hyperintensity on T2-weighted images and attributed these signal-intensity abnormalities to manganese accumulation in the CNS. However, these controversial MR imaging findings are quite different from the classic pattern of manganese accumulation causing increased T1 MR imaging signal intensity within the basal ganglia, especially in the globus pallidus.⁸⁻²¹ We agree that manganese accumulation within the basal ganglia induced parkinsonian symptoms secondary to an overload of this trace element from dietary intake, as postulated by the authors. However, the relationship between the previously mentioned signal-intensity abnormalities on MR imaging and elevated serum manganese levels was not established in this particular case. On the other hand, there are other metabolic dysfunctions induced by hemodialysis that cause MR imaging findings quite similar to those described by Ohtake et al,³⁷ such as the syndrome of acute bilateral basal ganglia lesions in patients with diabetic uremia³⁸ and osmotic demyelination syndrome in end stage renal disease after recent hemodialysis.^{39,40}

Myoclonus. Patient 4 presented a prominent myoclonus only in the right upper limb, causing motor dysfunction for more than 1 year.

The findings of neurologic examinations of the remaining patients were unremarkable.

Discussion

A biologic marker of manganese accumulation within the CNS is bilaterally increased T1 MR imaging signal intensity within the basal ganglia, especially in the globus pallidus.⁸⁻²¹ In patients undergoing hemodialysis, serum manganese concentration is reported to be low, compared with that in the healthy population,³² and the reason is thought to be removal of manganese from blood during hemodialysis. It, thus, theoretically is reasonable that manganese intoxication would be unlikely in patients undergoing hemodialysis if the dialysate is not severely contaminated by manganese. In our institution, the dialysate contains no detectable manganese. Therefore, manganese intoxication was not caused by contamination of the dialysate, unlike the case reported by Taylor and Price.³³ Manganese (Mn) circulates in the blood as Mn³⁺ bound tightly to transferrin or Mn²⁺ (the free ion or bound to such plasma proteins as albumin).³⁴ The main route of manganese excretion is thought to be through the biliary tract,³⁵ and urinary excretion is thought to be negligible.³⁶ Therefore, anuria caused by renal failure may not influence manganese metabolism.

To the best of our knowledge, this is the first time that manganese accumulation in the CNS has been demonstrated by MR imaging in patients undergoing maintenance hemodialysis. As suggested by Ohtake et al,³⁷ some possibilities exist with respect to abnormal manganese accumulation in this setting: disturbance of excretion through the biliary tract, increase in protein-bound (undiffusible) manganese that is not removed by hemodialysis, excessive manganese intake that exceeds the excretory capacity, and the effect of uremia on manganese metabolism. Biliary excretion was thought to be normal in our patients because none of them had liver dysfunction or biliary tract obstruction according to laboratory tests and abdominal ultrasonography, respectively. An elevated protein-binding rate of manganese also was thought to be unlikely. Although the exact level of protein binding could not be measured in these patients, it is reported to be decreased significantly in patients with uremia.⁴¹ Excessive manganese intake seems to be a plausible explanation even in the absence of oral supplements rich in this trace metal in our

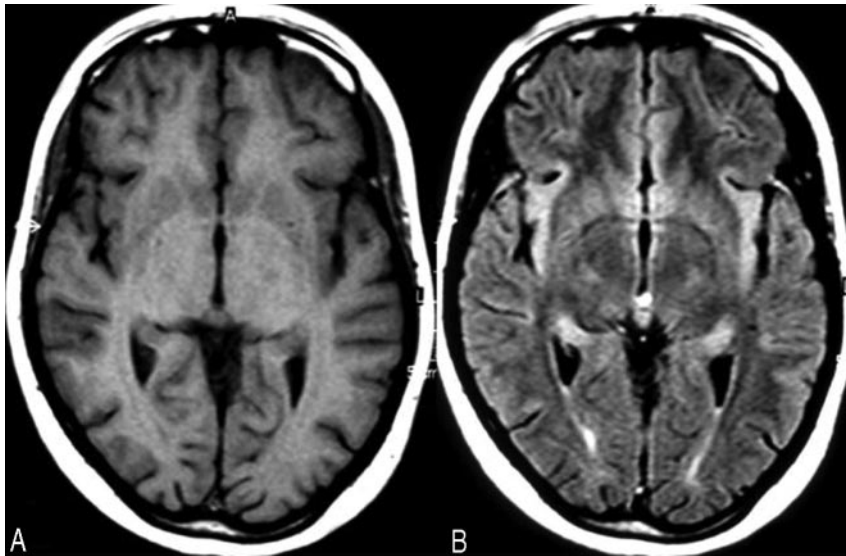


Fig 2. Patient 8. Axial T1-weighted (A) and FLAIR (B) images do not show any signal-intensity abnormality.

group of patients. Although 2 of our 4 patients without dialytic treatment had slightly elevated serum manganese levels, probably secondary to dietary intake, they did not have manganese accumulation in the basal ganglia demonstrated by MR imaging. However, all of our patients undergoing hemodialysis had elevated serum manganese levels and pallidal T1 hyperintensities demonstrated by MR imaging, even in patient 2, in whom the serum manganese elevation was discrete.

The absence of striking blood manganese elevations in the setting of clinical manganese toxicity is not unexpected.^{8,30} Although the behavior of manganese in the blood stream of humans has not been well characterized, available evidence suggests that measured serum manganese primarily reflects that which is protein bound. When circulating proteins are saturated, free manganese rapidly binds to other tissues or is rapidly excreted from the body.^{42,43} Thus, free manganese does not accumulate in the circulation.⁴⁴ Consequently, serum manganese levels do not correlate with the intensity of exposure.¹⁵ Theoretically, patients with hypoalbuminemia tend to present with low serum manganese levels. Despite the questions raised previously, our 2 individuals with hypoalbuminemia (patients 8 and 9) had high serum manganese levels. The reason for this finding remains unknown.

We believe that manganese dietary intake (excessive or not) is necessary for accumulation of manganese in the basal ganglia, notably within the globus pallidus. However, hemodialysis might play an important role in this setting. Our findings are in line with those reported by Schabowski et al,⁴⁵ who described the manganese content in patients undergoing long-term hemodialysis as significantly increased postmortem. The brain manganese level is reported to exceed that in plasma by more than 100-fold,⁴⁶ so selective binding or active transport may promote manganese uptake by the brain in patients undergoing long-term hemodialysis. Manganese transport channels include transferrin receptor-dependent binding or transport through the Ca^{2+} channel, $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger, and $\text{Na}^{+}/\text{Mg}^{2+}$ antiporter.³⁵ Particularly, the basal ganglia are the site of abundant transferrin receptors.³⁵ Some unknown mechanisms related to hemodialysis may lead to manganese accumulation in the brain of these patients, probably due to dysfunction of the previously mentioned manganese trans-

port channels. Although our understanding of the cellular compartmentalization of manganese under in vivo pathologic conditions is uncertain, in vitro findings indicate that glial cells possess a high-affinity transport mechanism for manganese⁴⁷ and have the capacity to accumulate manganese by up to 200 times the extracellular concentration.⁴⁸ Additional studies have revealed that 60%–70% of the accumulated manganese is sequestered in mitochondria, whereas the rest is localized to the cytosol.⁴⁹ Thus, current evidence suggests an involvement of mitochondria in astrocytes in the neuropathology of man-

gane neurotoxicity.

Quite similar to authors of a previous study,¹⁵ we observed heterogeneous symptoms in those 4 symptomatic patients undergoing hemodialysis. As previously described by Josephs et al,¹⁵ 2 clinical syndromes, parkinsonian symptoms and myoclonus, have also emerged in our preliminary results; parkinsonism has been reported in manganese toxicity by several authors.^{6,10,11,15-17,28-31} Myoclonus (depicted in patient 4) has only been documented in 3 patients with manganism so far.^{9,15} Although auditory and vestibular symptoms have been reported in manganese toxicity,^{30,50,51} they were not related to a particular syndrome, except by Josephs et al.¹⁵ Quite similar to this previous study, 1 of our patients (patient 1) undergoing hemodialysis had prominent vestibular-auditory symptoms associated with evident deficits on neurologic examination. Another presented evident vestibular symptoms confirmed by neurologic examination. Myoclonus and vestibular-auditory symptoms, though uncommon, seem to be plausible associations with manganism. Additionally, these symptoms never presented exacerbations during or immediately after dialytic procedures. However, the precise clinical spectrum of manganese neurotoxicity requires further studies and confirmation. Nevertheless, all symptoms were depicted only after an active search by an experienced neurologist.

Rodent data suggest that iron deficiency and anemia may be risk factors for manganese neurotoxicity.¹⁹ We have a small sample to perform a reliable statistical analysis among iron deficiency, anemia, and manganism. However, we considered serum hemoglobin levels below 10 g/dL as anemia in the setting of chronic nephropathy. In our series, we had 5 anemic individuals (patients 2, 4, 6, 7, and 9). Patients 2 and 4 presented symptoms of manganism (dialytic group). On the other hand, patients 1 and 5 were not anemic and also presented symptoms of manganese neurotoxicity (dialytic group). Patients 6, 7, and 9 were asymptomatic (nondialytic group). We think that there are not enough data to corroborate this association in our patients. The main risk factor for manganism seems to be maintenance hemodialysis in this setting.

Calcium deposits can accumulate in the basal ganglia of patients with chronic renal failure secondary to parathyroid

hyperfunction. Unfortunately, it is not possible to demonstrate any statistical difference in serum calcium levels between the dialytic and nondialytic groups because of the small number of patients. In previous studies, the presence of high signal intensity on T1-weighted images has been demonstrated in association with cerebral parenchymal calcification, possibly reflecting the incorporation of paramagnetic ions or altered effects of hydration.²⁵ Although CT studies in our patients undergoing hemodialysis demonstrated no change to correlate with regions of high pallidal MR signal intensity, the presence of increased calcium or other metal ions cannot be completely excluded. Postmortem analysis, not available in our series, would have been useful in evaluating these possibilities.

A limitation of our preliminary results is the small number of patients, but more individuals are being studied and an age- and sex-matched healthy control group will soon be included in this protocol. Without the widespread availability of dialysis and kidney transplantation, many lives would have ended prematurely; however, we consider our findings consistent enough to raise attention to manganese accumulation in the CNS in patients undergoing maintenance hemodialysis, causing symptoms related to manganism and increasing their morbidity.

Conclusion

Our preliminary results showed that the bilaterally increased T1 MR imaging signal intensity depicted in the globus pallidus of our patients undergoing hemodialysis could reflect manganese accumulation in the CNS, revealing a new association. Although this signal-intensity abnormality has a weak correspondence with high serum manganese levels, almost all patients undergoing hemodialysis showed signs attributable to manganism. The reason for this accumulation is yet unclear, probably related to both dysfunction of manganese transport channels facilitated by dialytic therapy and dietary intake of this trace metal. However, we have a limited number of patients, and our findings describe only an association. It would be necessary to provide further proof, such as evidence from postmortem pathology studies.

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This is the overview page

Manganese neurotoxicity in patients undergoing maintenance hemodialysis: a clinical, laboratory, and magnetic resonance imaging study.

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Key Words:	basal ganglia, dialysis, magnetic resonance imaging, manganese, manganese toxicity, renal failure

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3 Cover letter
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8 Dear Editor,
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11 We are very pleased to submit our article entitled "Manganese
12 neurotoxicity in patients undergoing maintenance hemodialysis: a clinical,
13 laboratory, and magnetic resonance imaging study" to this important journal.
14 Recently, we published an original research of Mn neurotoxicity associated with
15 maintenance hemodialysis in the American Journal of Neuroradiology.
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24 In the present article, our results confirmed that hemodialysis is related to
25 the presence of bilateral pallidal T1 MRI hyperintensity and to high serum Mn
26 levels in a larger series of patients, with further statistical analysis. We also
27 demonstrated that symptoms attributable to manganism occur frequently in
28 dialysis patients. We proposed a physiopathology to explain the above-
29 mentioned phenomena based on the current concepts concerning the transport
30 mechanisms of Mn in the serum and tissues.
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42 We also describe, for the first time, the progressive reversal of the
43 bilateral T1 hyperintensity in the globus pallidus and high serum Mn levels
44 following discontinuation of dialysis after successful renal transplantation.
45 Although the widespread availability of dialysis has prolonged many lives, we
46 consider our findings consistent enough to call attention to the risks of brain Mn
47 accumulation in dialysis patients, which include symptoms related to
48 manganism.
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3 Neither the manuscript nor any significant part of it is under consideration
4 for publication elsewhere, or has appeared elsewhere in a manner that could be
5 construed as a prior or duplicate publication of the same, or very similar, work.
6
7 All authors took part in the conception or design, or analysis and interpretation
8 of data, or both.
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17 Kindest regards,

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19 Carlos Jorge da Silva, MD.
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For Peer Review

TITLE PAGE

Manganese neurotoxicity in patients undergoing maintenance hemodialysis: a clinical, laboratory, and magnetic resonance imaging study.

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For Peer Review

ABSTRACT

Background: Patients undergoing parenteral nutrition, as well as those with portosystemic encephalopathy secondary to chronic liver disease, or with acquired and congenital portosystemic venous shunts frequently have manganese (Mn) deposition in basal ganglia. These deposits can be visualized by MRI as hyperintense areas on T1-weighted sequences. We observed similar abnormalities in the basal ganglia of patients with chronic renal failure undergoing maintenance hemodialysis. Our aims were to evaluate the pallidal signal intensity on T1 images in patients undergoing hemodialysis, further analyze serum Mn levels, and explore any neurological symptoms related to manganism. We compared these patients to patients with chronic renal failure not receiving dialysis and to normal controls. Methods: We performed MRI scans on 48 individuals; 16 were receiving hemodialysis (group 1), 16 had chronic renal failure but were not receiving dialysis (group 2), and 16 were normal controls (group 3). We examined the basal ganglia for evidence of symmetric areas of hyperintensity on T1, determined serum Mn levels, and performed neurological evaluations on all patients. Results: In group 1, all patients showed symmetric areas of pallidal hyperintensity on T1 and high serum Mn levels ($p < 0.001$); half exhibited neurological symptoms related to manganism ($p < 0.001$). No patients in groups 2 and 3 showed bilateral pallidal hyperintensity or symptoms of manganism. Conclusion: Our results confirmed a link between hemodialysis and the presence of bilateral pallidal hyperintensity on T1 images and with high serum Mn levels. We also confirmed that clinical symptoms attributable to manganism are common in patients undergoing hemodialysis.

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3 KEY WORDS: basal ganglia, dialysis, magnetic resonance imaging, manganese,
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5 manganese toxicity, renal failure.
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9 SHORT SUMMARY

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12 Chronic hemodialysis is related to the presence of bilateral areas of pallidal
13 hyperintensity on T1 images as well as to high serum Mn levels. We confirmed that
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15 clinical symptoms attributable to Mn neurotoxicity are common in patients undergoing
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17 hemodialysis.
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INTRODUCTION

Patients receiving total parenteral nutrition, those with portosystemic encephalopathy secondary to chronic liver disease, and those with acquired and congenital portosystemic venous shunts frequently present with manganese (Mn) accumulation in the adenohypophysis and other regions of the brain, including the globus pallidus, putamen, subthalamic region, substantia nigra, and the hemispheric white matter [1-7]. A marker of Mn accumulation in the brain is the presence of bilateral T1 MRI hyperintensity within the basal ganglia, particularly in the globus pallidus [4-14]. Some authors have described the same pattern of Mn accumulation in the brains of welders secondary to the inhalation of ambient welding fumes rich in this trace metal [10-12]. Manganism commonly presents as a parkinsonian syndrome [6, 8, 10-13]. However, manganese toxicity has also been variously described as a syndrome of multifocal myoclonus and limited cognitive impairment, a mixed syndrome with vestibular-auditory symptoms, and a minor syndrome with subjective cognitive impairment, anxiety, and sleep apnea [10, 12, 13]. Recently, the above-mentioned MRI findings and symptom patterns were also documented in patients undergoing maintenance hemodialysis [13]. The cause of these findings is not yet clear, and we presume that these symptoms and MRI signal abnormalities may reflect the presence of Mn accumulation in the brain.

Our aims were to evaluate pallidal signal intensity in T1-weighted images, to determine serum Mn levels, and to depict any potential neurological symptoms related to manganism in a series of patients undergoing maintenance hemodialysis. We

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3 compared these individuals to patients with chronic renal failure not undergoing dialysis
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5 as well as to normal controls. Our series includes one patient who experienced reversal
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7 of brain Mn deposition and high serum Mn levels following successful renal
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9 transplantation and discontinuation of dialysis treatment over a one-year follow-up
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11 period.
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15 16 SUBJECTS AND METHODS 17

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20 Our Institutional Review Board approved this study, and we obtained informed
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22 consent from all subjects. Our hemodialysis unit is operated in accordance with the laws
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24 of The Ministry of Health. We divided the individuals in group 1 (patients with chronic
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26 renal failure undergoing maintenance hemodialysis); group 2 (patients with chronic
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28 renal failure not undergoing dialysis); and group 3 (normal controls). We performed a
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30 non-enhanced brain MRI using a 1.0-T scanner and obtained serum Mn levels from all
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32 individuals by means of atomic absorption spectrophotometry (with values >0.85 ng/mL
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34 defined as elevated). An experienced neurologist (MFM), who was blinded to imaging
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36 and serum data, performed the neurological evaluations of all individuals.
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43 The non-enhanced brain MRI images were obtained using axial slices covering
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45 the whole brain and aligned with the bicommissural line. Imaging parameters were
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47 identical in all examinations (24 cm FOV, 6 mm thickness, 0.6 mm gap, 205x512
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49 matrix). Our protocol included axial turbo spin-echo (TSE) fluid-attenuated inversion
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51 recovery (FLAIR) sequences (TR 11000 ms, TE 140 ms, TI 2600 ms, TSE factor 29)
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53 and spin-echo (SE) acquisition to obtain T1-weighted images (TR 509 ms, TE 14 ms).
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55 We also obtained an axial T2* sequence (TR 615 ms, TE 21 ms, flip angle 15).
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3 Patients in groups 1 and 2 had blood studies performed, including a complete
4 blood count, chemistry profile, albumin level, bilirubin level, hepatitis B and C screening,
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6 HIV screening, iron studies, thyroid and parathyroid panels, and liver and renal function
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8 tests.
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14 In group 1, we also performed an axial non-enhanced brain computed
15 tomography (CT) scan and an abdominal Doppler ultrasonography.
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20 The inclusion criteria for groups 1 and 2 were the following: willing participation in
21 the study; serum creatinine level >1.5 mg/dL; and creatinine clearance <60 mL/min. In
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23 group 1, we only included patients who had received more than two years of
24
25 hemodialysis.
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30 The exclusion criteria for this study were as follows: contraindication to MRI; viral
31 infection with hepatitis B, C, or HIV; hepatic failure; hepatic portosystemic venous shunt
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33 or biliary obstruction on abdominal Doppler ultrasonography; elevated serum bilirubin
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35 levels; prominent calcifications in the globus pallidus on CT; prominent ferromagnetic
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37 deposits in the globus pallidus on MRI; history of receiving total parenteral nutrition;
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39 alcoholism; and history of welding.
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46 Between January 2006 and June 2009, we consecutively enrolled 48 individuals,
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48 with 16 in each group. An experienced neuroradiologist (AJR), who was blinded to the
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50 clinical and serum data, analyzed the MRI and CT scans of each patient independently.
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54 In our statistical analysis, we compared age, gender, MRI findings, serum Mn
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56 levels, and neurologic evaluations of the patients in group 1 with those of the patients in
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3 groups 2 and 3. We also evaluated the possible association between manganese and
4 low serum hemoglobin, ferritin, iron, and transferrin saturation. We analyzed the
5 qualitative data as simple and relative (percentage) frequencies and determined the
6 mean value and standard deviation (SD) for quantitative data. We used analysis of
7 variance (ANOVA) to compare quantitative data between groups and Pearson's χ^2 test
8 or Fisher's exact test for comparisons of qualitative data. We used SPSS for Windows,
9 version 17.0, for all statistical analyses. The significance level was 0.05.
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21 We performed four brain MRI scans between November 2007 and October 2008
22 in one patient from group 1 who underwent successful cadaveric renal transplantation.
23 We obtained the first scan two days before renal transplantation (baseline) and the
24 other three scans at four-month intervals. We also measured her Mn levels concurrent
25 with each MRI scan.
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34 RESULTS

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37 We summarized the clinical data, serum Mn levels, and MRI results in Table 1.
38 Table 2 compares the three groups with respect to age, gender, clinical features, serum
39 Mn levels, and MRI findings. All analyzed variables shown in Table 2, except gender
40 ($p=0.715$), differed significantly between groups. The patients in group 2 were
41 significantly older than patients in the other two groups, and group 3 patients were
42 significantly younger than the other groups. However, when we analyzed the mean age
43 of groups 2 and 3 together (38.5 y, SD=17.4), the pooled mean age did not differ
44 significantly from the mean age of group 1 (36.3 y, SD=11.3, $p=0.609$). For those
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3 remaining variables in Table 2, group 1 still differed significantly ($p < 0.001$) from groups
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5 2 and 3 combined.
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9 All of the patients in group 1 ($n=16$) had high serum Mn levels and bilateral
10 pallidal hyperintensity on T1 (Figure 1). Half of them ($n=8$) exhibited symptoms
11 attributable to manganism. Patients in groups 2 and 3 did not possess either these MRI
12 findings (Figure 2) or symptoms of manganism. Thus, patients in group 1 differed
13 significantly from patients in groups 2 and 3 with respect to these parameters.
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22 Table 3 compares the 8 symptomatic patients in group 1 with the remaining 24
23 patients with chronic renal failure with respect to values for serum hemoglobin, ferritin,
24 iron, and transferrin saturation. There were no statistical differences identified between
25 any of the above-mentioned variables. However, the power of the test was only 31%
26 ($\geq 80\%$ is desirable) due to the limited number of patients.
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35 Although the patients in group 1 showed a wide range of serum calcium levels
36 (not shown), none had prominent calcifications on CT scans or prominent ferromagnetic
37 deposits on T2* sequences in the globus pallidus that correlated to the more extensive
38 areas of pallidal hyperintensity that were seen on the T1-weighted images.
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46 The remaining blood studies were unremarkable. None of our patients received
47 oral vitamin supplements that were rich in Mn. In groups 1 and 2, all patients were
48 placed on fluid restricted and low-potassium, low-sodium diets. They were also given
49 oral vitamin B and folic acid supplements. In group 2, the patients were put on a low-
50 protein diet.
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3 Before renal transplantation, the baseline MRI scan of patient 14 showed
4 bilateral pallidal T1 hyperintensity (Figure 3A). After renal transplantation, her three
5 follow-up MRI scans (Figure 3B-D) revealed resolution of these lesions over a one-year
6 period (based on MRI scans at 4, 8, and 12 months). Her serum Mn levels progressively
7 returned to normal over an eight-month period (baseline=1.21 ng/mL, 4-month
8 visit=0.96 ng/mL, and 8- and 12-month visits=<0.5 ng/mL each).
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18 DISCUSSION

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22 A radiological marker of Mn accumulation in the brain is the presence of bilateral
23 T1 hyperintensity within the basal ganglia, particularly in the globus pallidus [4-14].
24 Although areas of T1 hyperintensity in these nuclei may be seen in several different
25 clinical conditions, including non-ketotic hyperglycemic episodes, hypoxia, type 1
26 neurofibromatosis, Wilson's disease, the early phase of kernicterus, hemorrhage, and
27 calcium deposits, this is a relatively uncommon pattern [15-20]. In fact, calcium deposits
28 can accumulate in basal ganglia of patients with chronic renal failure secondary to
29 parathyroid over activity. In previous studies, the presence of areas of pallidal T1
30 hyperintensity has been shown to be associated with cerebral parenchymal calcification,
31 possibly reflecting the incorporation of paramagnetic ions or the effects of altered
32 hydration [20]. However, the CT scans of our dialysis patients did not depict prominent
33 calcifications, and the T2* sequences did not show prominent ferromagnetic deposits in
34 the basal ganglia that correlated with the regions of pallidal T1 hyperintensity. These
35 arguments support the hypothesis that brain Mn accumulation is responsible for the
36 bilateral pallidal T1 hyperintensity seen in all of the patients in group 1. However, the
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3 possibility that these findings represent the deposition of calcium or other metal ions
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5 cannot be completely excluded. Postmortem analysis, which was not available in our
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7 series, would have been useful in evaluating this theory.
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11 In addition, half of the patients in group 1 exhibited symptoms attributable to
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13 manganism. The areas of pallidal T1 hyperintensity and their progressive
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15 disappearance after successful renal transplantation were coincident with the
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17 progressive decrease of the high serum Mn levels in the one patient who underwent
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19 renal transplantation in this series. This finding also argues in favor of our hypothesis
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21 that Mn is the trace metal responsible for this MRI finding.
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27 Data from rodent studies suggest that iron deficiency and anemia may be risk
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29 factors for Mn neurotoxicity [21]. Our study did not show a statistically significant
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31 difference between the 8 symptomatic patients in group 1 and the remaining 24 patients
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33 with chronic renal failure with respect to low serum hemoglobin, ferritin, iron, or
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35 transferrin saturation. However, the power of the test was only 31% ($\geq 80\%$ is desirable)
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37 due to the limited number of patients. We do not think there are enough data to support
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39 this association in our patients. Again, the reversal of the pallidal T1 hyperintensity and
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41 high serum Mn levels that we observed was coincident with the discontinuation of
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43 dialysis after renal transplantation. Based on these findings, the main risk factor for
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45 manganism seems to be maintenance hemodialysis.
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52 Recently, Ohtake et al. [22] described Mn-induced parkinsonism in a man with
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54 diabetic nephropathy undergoing maintenance hemodialysis. In this case, the source of
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56 Mn accumulation was intake of an oral supplement that was rich in this trace metal.
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3 However, the controversial MRI findings described by these authors are quite different
4 from the classic pattern of Mn accumulation causing pallidal T1 hyperintensity [4-14].
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6 Thus, the relationship between signal-intensity abnormalities on MRI and elevated
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8 serum Mn levels was not established in this particular case.
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14 More recently, da Silva et al. [13] described the classic MRI findings of Mn
15 accumulation in the brains of patients undergoing maintenance hemodialysis without
16 any identifiable dietary source of Mn. A number of potential etiologies exist with respect
17 to abnormal Mn accumulation in the setting of chronic renal failure and hemodialysis.
18
19 Possible causes include the disturbance of Mn excretion by the biliary tract, the effect of
20 uremia on Mn metabolism, Mn intoxication due to dialysate contamination, excessive
21 Mn intake exceeding the excretory capacity of the liver, and low Mn-transferrin binding
22 capacity in the serum of dialysis patients.
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34 Mn circulates in the blood either as Mn^{3+} , which is bound tightly to transferrin (the
35 major Mn plasma carrier), or Mn^{2+} , which is present either as a free ion or bound to
36 plasma proteins such alpha-2-macroglobulin [23]. The main route of Mn excretion is
37 believed to be through the biliary tract [24]. Biliary excretion was thought to be normal in
38 our patients because they had neither liver dysfunction nor biliary tract obstruction
39 according to the results of their laboratory tests and abdominal ultrasonography,
40 respectively. Thus, disturbance of Mn excretion by the biliary tract is not a plausible
41 hypothesis for Mn accumulation among the patients in group 1.
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54 We reached the same conclusion about the possible effect of uremia on Mn
55 metabolism, since urinary Mn excretion is thought to be negligible [25]. Therefore,
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3 anuria caused by renal failure likely does not influence Mn metabolism in a meaningful
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5 way.
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9 It is reasonable to hypothesize that Mn intoxication would be unlikely in patients
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11 undergoing hemodialysis if the dialysate is not severely contaminated by Mn. In our
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13 institution, the dialysate is in accordance to the laws of purity of The Ministry of Health
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15 and contains no detectable Mn. Therefore, Mn intoxication was not caused by
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17 contamination of the dialysate, unlike in the case reported by Taylor and Price [26].
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21 While excessive Mn intake seems to be a plausible explanation for Mn
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23 intoxication, our patients received neither oral supplements nor a diet rich in this trace
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25 metal. All of the patients in group 1 had high serum Mn levels ($p < 0.001$). Although four
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27 (25%) of the patients in group 2 and eight (50%) of the patients in group 3 also had
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29 elevated serum Mn levels, neither of them exhibited pallidal T1 hyperintensity or
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31 symptoms of manganism. We think that dietary intake explains the presence of serum
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33 Mn in all of our subjects but not the high serum levels and brain accumulation that was
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35 present in all of the patients in group 1.
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43 Although the characteristics of Mn in the bloodstream have not been well
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45 defined, available evidence suggests that serum Mn measurements primarily reflect the
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47 proportion of Mn that is protein-bound. When the circulating Mn-binding proteins are
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49 saturated, free Mn is excreted from the body in normal individuals or rapidly binds to
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51 other tissues [27, 28]. Thus, free Mn does not accumulate in the serum. Consequently,
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53 serum Mn levels correlate with transferrin saturation and not with the intensity of the Mn
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55 exposure [10]. Therefore, the reason that all of the patients in group 1 exhibited high
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3 Mn-transferrin saturation and the correlation between this and the brain Mn
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5 accumulation that was observed in those individuals remains unclear.
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9 Serum Mn concentration is generally reported to be low in patients undergoing
10 hemodialysis as compared to the levels that are seen in the healthy population, but data
11 on this topic are scarce [29]. Although we did not assess the Mn-transferrin binding
12 capacity of subjects, this parameter is reported to be decreased significantly in patients
13 undergoing maintenance hemodialysis [30]. Consequently, we believe that a higher
14 concentration of free Mn, which cannot be determined through serum Mn examinations,
15 would exceed the liver's excretory capacity and accumulate in tissues. Based on these
16 arguments, we think that the decreased Mn-transferrin binding capacity that was
17 present in the serum of dialysis patients is the most plausible explanation for the Mn
18 accumulation that was observed in the brains of all of the group 1 patients. Our findings
19 are in line with those reported by Schabowski et al. [31], who found that the Mn content
20 of patients who received long-term hemodialysis were significantly increased
21 postmortem. Brain Mn levels exceed that in plasma levels more than 100-fold [32],
22 suggesting that selective binding or transport may promote Mn uptake by the brain in
23 long-term hemodialysis patients.
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45 When tissue saturation occurs, we believe that the Mn concentration in the
46 tissues reaches equilibrium with that in the plasma, allowing further overload of free Mn
47 in the serum. We believe that this additional overload of free Mn in the serum would
48 lead to transferrin saturation over the years, despite the decreased Mn-transferrin
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3 binding capacity of dialysis patients. After years of hemodialysis, patients' sera Mn
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5 levels would therefore become elevated due to Mn-transferrin saturation.
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9 It is important to note that the basal ganglia are sites of abundant transferrin
10 receptors [33]. Inside the neuron, Mn is rapidly taken up by the mitochondria where it
11 promotes calcium accumulation by inhibiting both the sodium-dependent and sodium-
12 independent calcium exporter [34]. Mn also interferes with oxidative phosphorylation by
13 inhibiting mitochondrial F1-ATPase [35], resulting in the depletion of ATP [36].
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22 Sims et al. showed that Mn preferentially damages the GABAergic neurons in the
23 globus pallidus [37], but it is unclear why neurons within the globus pallidus are the
24 selective target of Mn. The most likely explanation for this relates to differences in the
25 synapsing neurons at the two sites. Only the globus pallidus selectively receives
26 glutaminergic input from the subthalamic nuclei [38, 39]. Glutamate is an excitatory
27 neurotransmitter and it is potentially capable of exacerbating the actions of Mn as the
28 toxic mechanisms of the two are similar [40]. Glutamate toxicity is caused by an
29 increase in intracellular Ca^{2+} or Mn^{2+} initiated by binding of glutamate to its ionotropic
30 receptor [41]. The accumulated intracellular Ca^{2+} is also taken up into the mitochondria
31 via the Ca^{2+} uniporter, where it is sequestered and provokes changes in mitochondrial
32 membrane permeability, ultimately leading to intracellular cytotoxic signaling and cell
33 death [42]. It is generally accepted that Mn-induced neurotoxicity is mediated by the
34 disruption of mitochondria, which leads to the initiation of both apoptosis and necrotic
35 cell death via formation of highly reactive oxygen species [43].
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3 Not all of the patients in group 1 exhibited symptoms of manganism. One patient
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5 with only three years of hemodialysis exposure presented with parkinsonism, whereas
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7 another patient with seven years of exposure was asymptomatic. These findings are
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9 consistent with the known inter-individual variations in susceptibility to Mn
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11 overexposure. The divalent metal transporter 1 (DMT1) is generally regarded as the
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13 major Mn transporter protein [43]. The primary mode for Mn uptake by the cells involves
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15 either a transferrin-dependent or transferrin-independent pathway, both of which utilize
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17 DMT1 as the transmembrane carrier [44]. Since Mn transport by DMT1 is likely to be
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19 the rate limiting step that controls toxicity, it is important to understand the factors that
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21 contribute to its expression in vivo. Four isoforms of DMT1 encoded by a single gene
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23 have been identified in mammalian cells [45]. Several studies indicate that these four
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25 are differentially localized in organelles and in distinct endosomal vesicles within cells
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27 [45]. The unique and selective distribution of these isoforms implies they likely have
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29 discrete physiological functions and, most importantly, diverse regulatory processes
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31 controlling their expression [46]. These arguments could explain the differences in
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33 susceptibility to Mn overexposure observed in our patients.
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42 The reasons for the high serum Mn levels and brain Mn accumulation that are
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44 present in dialysis patients have not yet been fully elucidated, and the proposed
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46 physiopathology needs to be validated in experimental models. We did not perform
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48 postmortem analysis to measure the concentration of Mn or other trace elements in the
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50 globus pallidus. In addition, we had too few symptomatic patients to allow a reliable
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52 statistical analysis examining the correlation between iron deficiency and anemia to the
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54 occurrence of symptoms of manganism. Our report suggests that these pathological
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3 processes might be interrupted following successful renal transplantation and cessation
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5 of the dialysis. However, these issues need to be examined in further studies with larger
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7 patient populations as well as in experimental models.
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10 11 *Conclusions*

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15 Our results confirmed that hemodialysis is related to the presence of bilateral
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17 pallidal T1 hyperintensity and to high serum Mn levels. These findings can be
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19 progressively reversed following discontinuation of dialysis after successful renal
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21 transplantation. We also demonstrated that clinical symptoms attributable to manganism
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23 occur frequently in dialysis patients. Although the widespread availability of dialysis has
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25 prolonged many lives, we consider our findings consistent enough to call attention to the
26
27 risks of brain Mn accumulation in dialysis patients, which include symptoms related to
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29 manganism.
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34 35 **ACKNOWLEDGMENTS**

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38 We would like to thank Fleury Medicina e Saúde for determining the serum Mn levels of
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40 all included subjects.
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44 45 **TRANSPARENCY DECLARATION**

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48 None of the authors have any competing financial interests.
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51 52 **CONFLICT OF INTEREST STATEMENT**

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55 We declare that the results presented in this paper have not been published previously
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TABLES

Table 1: Clinical data, serum Mn levels, and MRI results of all patients.

Patient	Group	Sex	Age (y)	Mn (ng/mL)	Clinical features	MRI
1	1	F	48	1.18	parkinsonism and a mixed syndrome with prominent vestibular-auditory symptoms	pallidal hyperintensities on T1
2	1	M	33	0.86	vestibular syndrome	pallidal hyperintensities on T1
3	1	M	27	0.98	unremarkable	pallidal hyperintensities on T1
4	1	M	45	2.24	myoclonus	pallidal hyperintensities on T1
5	1	M	43	1.35	parkinsonism	pallidal hyperintensities on T1
6	1	F	23	1.36	parkinsonism	pallidal hyperintensities on T1
7	1	M	45	1.17	unremarkable	pallidal hyperintensities on T1
8	1	F	58	0.9	unremarkable	pallidal hyperintensities on T1
9	1	M	50	1.79	parkinsonism and vestibular syndrome	pallidal hyperintensities on T1
10	1	M	34	1.19	unremarkable	pallidal hyperintensities on T1
11	1	M	22	1.27	unremarkable	pallidal hyperintensities on T1
12	1	F	41	1.28	unremarkable	pallidal hyperintensities on T1
13	1	F	28	0.87	parkinsonism	pallidal hyperintensities on T1
14	1	F	18	1.21	unremarkable	pallidal hyperintensities on T1
15	1	F	33	1.53	unremarkable	pallidal hyperintensities on T1
16	1	F	33	2.28	parkinsonism	pallidal hyperintensities on T1
17	2	F	74	0.62	unremarkable	normal
18	2	F	62	0.77	unremarkable	normal
19	2	F	22	0.99	unremarkable	normal
20	2	M	38	0.87	unremarkable	normal
21	2	F	21	1.24	unremarkable	normal
22	2	M	60	0.81	unremarkable	normal
23	2	F	31	0.85	unremarkable	normal
24	2	F	35	1.54	unremarkable	normal
25	2	F	33	0.68	unremarkable	normal
26	2	F	65	0.4	unremarkable	normal
27	2	M	61	0.55	unremarkable	normal
28	2	F	54	0.52	unremarkable	normal
29	2	M	52	0.3	unremarkable	normal
30	2	F	55	0.82	unremarkable	normal
31	2	M	65	0.61	unremarkable	normal
32	2	M	77	0.84	unremarkable	normal
33	3	F	27	0.71	unremarkable	normal
34	3	F	27	0.88	unremarkable	normal
35	3	M	32	0.93	unremarkable	normal
36	3	M	25	0.84	unremarkable	normal
37	3	M	25	1.29	unremarkable	normal
38	3	F	25	1.2	unremarkable	normal

39	3	M	29	0.7	unremarkable	normal
40	3	F	29	0.65	unremarkable	normal
41	3	M	26	1.23	unremarkable	normal
42	3	F	30	1.68	unremarkable	normal
43	3	M	26	0.5	unremarkable	normal
44	3	M	26	1.08	unremarkable	normal
45	3	F	25	1.23	unremarkable	normal
46	3	M	24	0.54	unremarkable	normal
47	3	F	25	0.76	unremarkable	normal
48	3	F	25	0.66	unremarkable	normal

Table 2: Comparisons among the 3 groups.

Variables	Group			p-value
	1 (n=16)	2 (n=16)	3 (n=16)	
Gender – n (%)				
Female	8 (50%)	10 (62.5%)	8 (50%)	0.715
Male	8 (50%)	6 (37.5%)	8 (50%)	
Age (y) - mean (sd)	36.3 ^{ab} (11.3)	50.3 ^a (17.9)	26.6 (2.3)	<0.001
Clinical features – n (%)				
Unremarkable	8 (50%)	16 (100%)	16 (100%)	<0.001
Mn neurotoxicity	8 (50%) ^{ab}	-	-	
Mn (ng/mL) – mean (sd)	1.34 ^{ab} (0.43)	0.78 (0.31)	0.93 (0.33)	<0.001
High serum Mn level – n (%)	16 (100%) ^{ab}	4 (25%)	8 (50%)	<0.001
MRI findings – n (%)				
Normal	-	16 (100%)	16 (100%)	<0.001
Abnormal	16 (100%) ^{ab}	-	-	

^a p<0.05 when compared to group 3; ^b p<0.05 when compared to group 2.

Table 3: Comparisons of blood studies between the symptomatic and asymptomatic chronic renal failure patients

Variables	Clinical features		
	asymptomatic (n=24)	symptomatic (n=8)	p-value
Hemoglobin (g/dL)			
Mean (sd)	10.2 (1.6)	9,9 (1.7)	0.690
Low – n (%)	9 (37.5%)	4 (50.0%)	0.684
Ferritin (µg/L)			
Mean (sd)	245.4 (153.4)	376.9 (213.4)	0.067
Low – n (%)	10 (41.7%)	4 (50.0%)	0.703
Transferrin saturation (%)			
Mean (sd)	23.8 (16.5)	22.6 (11.0)	0.859
Low – n (%)	12 (50.0%)	4 (50.0%)	>0.999
Iron (µg/dL)			
Mean (sd)	56.5 (28.0)	46,0 (16.5)	0.324
Low – n (%)	13 (54.2%)	6 (75.0%)	0.420

LEGENDS TO FIGURES

Figure 1. Patient 16 (group 1). Axial T1-weighted images show bilateral and symmetric hyperintensities within the globus pallidus (A) and substantia nigra (B) (arrows). Corresponding axial T2* (C-D) and CT (E-F) images are normal.

Figure 2. Patient 25 (group 2). Axial T1-weighted images at the same level of patient 16 do not show any signal-intensity abnormality within the globus pallidus (A) and

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3 substantia nigra (B).
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8 Figure 3. Patient 14 (group 1). Axial T1-weighted images (A-D). Baseline examination
9 (A) shows bilateral and symmetric hyperintensities within the globus pallidus (arrows).
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11 Follow-up examinations after 4 (B), 8 (C), and 12 (D) months show the progressive
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13 disappearance of those bilateral and symmetric hyperintensities (arrows).
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For Peer Review

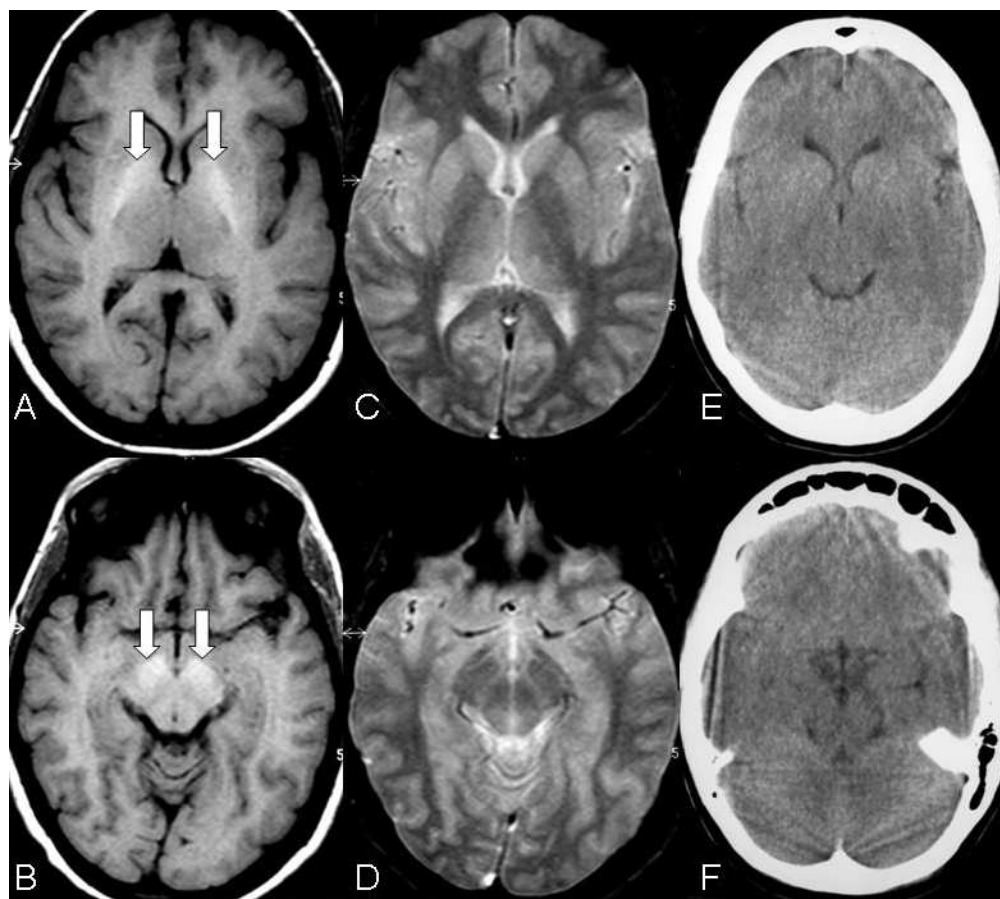


Figure 1. Patient 16 (group 1). Axial T1-weighted images show bilateral and symmetric hyperintensities within the globus pallidus (A) and substantia nigra (B) (arrows). Corresponding axial T2* (C-D) and CT (E-F) images are normal.
66x59mm (300 x 300 DPI)

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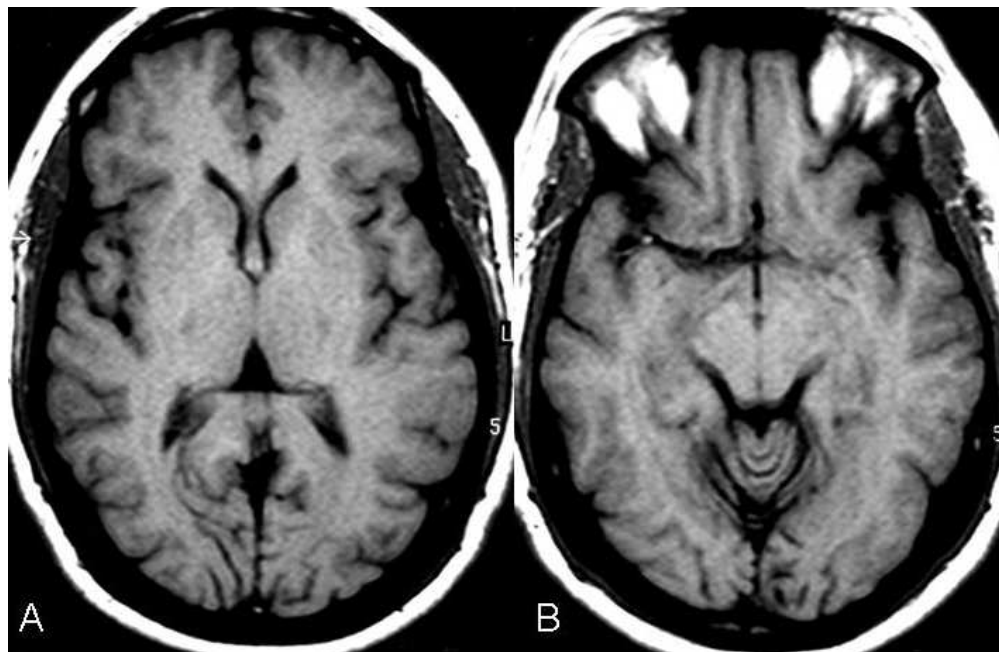


Figure 2. Patient 25 (group 2). Axial T1-weighted images at the same level of patient 16 do not show any signal-intensity abnormality within the globus pallidus (A) and substantia nigra (B). 60x38mm (300 x 300 DPI)

Review

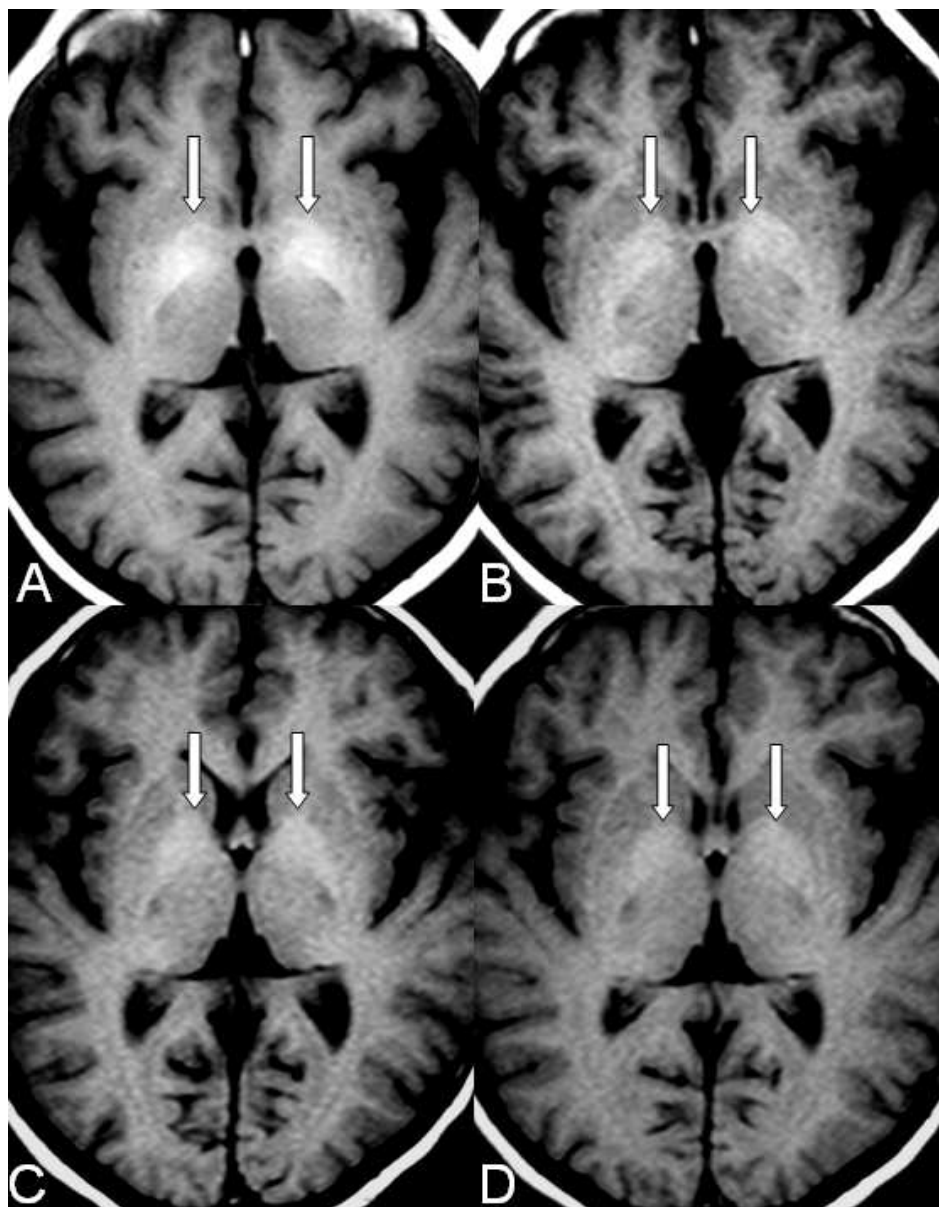


Figure 3. Patient 14 (group 1). Axial T1-weighted images (A-D). Baseline examination (A) shows bilateral and symmetric hyperintensities within the globus pallidus (arrows). Follow-up examinations after 4 (B), 8 (C), and 12 (D) months show the progressive disappearance of those bilateral and symmetric hyperintensities (arrows).
47x60mm (300 x 300 DPI)

Nossos resultados confirmam que a hemodiálise está relacionada à ocorrência do hipersinal simétrico nos globos pálidos, detectado nas sequências ponderadas em T1 de RM, correlacionando-se a altos níveis séricos de Mn. Nós também confirmamos que sintomas atribuíveis ao manganismo são frequentes neste grupo de pacientes.

Sem a disponibilidade da hemodiálise e do transplante renal, muitas vidas teriam terminado prematuramente. Entretanto, consideramos nossos achados suficientemente relevantes para demonstrar a ocorrência do acúmulo de Mn no encéfalo de pacientes submetidos à hemodiálise crônica, causando sintomas relacionados ao manganismo, aumentando a morbidade destes indivíduos. Nosso estudo aponta para a potencial reversibilidade do acúmulo de Mn no encéfalo de pacientes em hemodiálise com a interrupção do tratamento dialítico e o restabelecimento da função renal. Contudo, outros estudos serão necessários para essa definição.

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ANEXO 1

APROVAÇÃO DO COMITÊ DE ÉTICA



IRMANDADE DA SANTA CASA DE MISERICÓRDIA DE SÃO PAULO
COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS
 Rua Dr. Cesário Mota Júnior, 112 Santa Cecília CEP 01277900 São Paulo –SP
 PABX (11) 21767000 Ramais:57102/5502 – Fax- 2176.7041 E-mail: eficamed@santacasasp.org.br

São Paulo, 11 de abril de 2006.

Projeto nº098/06
 Informe este número para
 identificar seu projeto no CEP

Ilmo.(a).Sr.(a).

Dr.(a). Carlos Jorge da Silva
 Departamento de Medicina

O Comitê de Ética em Pesquisa da ISCMSP, reunido no dia **22/02/2006** e no cumprimento de suas atribuições, após revisão do seu projeto de pesquisa: **“Avaliação dos núcleos da base de pacientes renais crônicos em hemodiálise através de ressonância magnética e sua correlação com a dosagem sérica de manganês”** emitiu parecer inicial em pendência e nesta data enquadrando-o na seguinte categoria:

- Aprovado (inclusive TCLE);**
- Com pendências** (há modificações ou informações relevantes a serem atendidas em 60 dias, enviar as alterações em duas cópias);
- Retirado**, (por não ser reapresentado no prazo determinado);
- Não aprovado:** e
- Aprovado** (inclusive TCLE -Termo de Consentimento Livre e Esclarecido), e encaminhado para apreciação da Comissão Nacional de Ética em Pesquisa – MS -CONEP, a qual deverá emitir parecer no prazo de 60 dias. **Informamos, outrossim, que, segundo os termos da Resolução 196/96 do Ministério da Saúde a pesquisa só poderá ser iniciada após o recebimento do parecer de aprovação da CONEP.**



Prof. Dr. Daniel R. Muñoz

Presidente do Comitê de Ética em Pesquisa
 ISCMSP

ANEXO 2

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Prezado paciente,

Você está sendo convidado a participar de um estudo realizado na Santa Casa de São Paulo. Ele será conduzido sob a responsabilidade do investigador principal dessa instituição, Dr. Carlos Jorge da Silva (médico segundo assistente do Serviço de Diagnóstico por Imagem da Santa Casa, CRM 89017). Antes de decidir se irá participar desse trabalho, é importante que você entenda por que essa pesquisa está sendo realizada e como será seu envolvimento. O médico desse estudo responderá a todas as questões que você possa ter. O título dessa pesquisa é “Avaliação dos núcleos da base de pacientes renais crônicos em hemodiálise através de ressonância magnética e sua correlação com a dosagem sérica de manganês”, que tem como objetivo avaliar, através da ressonância magnética, alterações no cérebro (especificamente nas estruturas denominadas núcleos da base) de pacientes renais crônicos, em tratamento clínico e dialítico (hemodiálise), comparando os padrões encontrados com as dosagens de manganês sérico e com a avaliação clínica dirigida. Pretendemos identificar qual a origem da alteração metabólica (acúmulo de manganês no cérebro), caso esta venha a ser confirmada neste grupo de indivíduos e sugerir alterações dos processos de tratamento hoje praticados, caso sejam confirmados os passos responsáveis pela alteração metabólica, o que certamente teria um importante impacto do ponto de vista de saúde pública nesse contexto. Os benefícios de se participar desse estudo incluem um monitoramento mais detalhado da doença (insuficiência renal), com a realização de exames de ressonância magnética, tomografia computadorizada e ultra-sonografia abdominal com Doppler. Se você está em hemodiálise, realizaremos os 3 exames acima mencionados uma única vez, sem o uso de contraste endovenoso. Se você não está em hemodiálise, fará apenas ressonância magnética do crânio sem contraste. Todos os pacientes deverão colher sangue uma vez para a dosagem de manganês no laboratório Fleury e passarão em consulta neurológica para uma avaliação clínica dirigida para a detecção de eventuais sintomas causados pelo acúmulo de manganês. A ressonância magnética é um procedimento que usa campos magnéticos e ondas de rádio (mas não raios-X), para obter imagens do cérebro. A ressonância pode ser um método bastante barulhento e algumas pessoas podem se sentir desconfortável enquanto estão deitadas no aparelho. A tomografia computadorizada utiliza-se de raios-X para a formação das imagens, com uma dose baixa de radiação. Atenção: se houver suspeita ou comprovação de gravidez, a paciente deve nos informar imediatamente, antes da realização dos exames. Cabe somente a você participar ou não desse estudo. Se decidir não participar, você continuará a receber os cuidados médicos habituais do seu clínico. Se concordar em participar, você terá o direito de retirar-se a qualquer momento sem explicações e sem que isso tenha qualquer efeito nos cuidados médicos futuros. O pesquisador do estudo também lhe fornecerá quaisquer informações novas que possam afetar sua decisão em permanecer no estudo. As informações obtidas no estudo serão armazenadas e processadas para fins de avaliação científica. O Comitê de Ética em Pesquisa/Comissão Nacional de Ética em Pesquisa terão permissão para examinar os seus dados de estudo e registros médicos a fim de verificar se o estudo está sendo realizado adequadamente e de que você deu seu total consentimento (todas essas pessoas estão sujeitas a um termo de sigilo). Se os resultados do estudo forem publicados, sua identidade será mantida em sigilo.

Afirmo que fui convenientemente esclarecido pelo pesquisador e que entendi o que me foi explicado, de modo que concordo em participar da pesquisa.

São Paulo, ____ de _____ de _____

Nome do paciente por extenso

Assinatura

Nome do pesquisador por extenso

Assinatura

Dados do pesquisador:

Dr. Carlos Jorge da Silva CRM 89017

Médico Segundo Assistente do Serviço de Diagnóstico por Imagem da Santa Casa

Endereço: Rua Carlos Weber 457, apto 62B.

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