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Diffusion abnormalities of the globi pallidi in manganese neurotoxicity

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Abstract Manganese is an essential trace metal required for normal central nervous system function, which is toxic when in excess amounts in serum. Manganese neurotoxicity has been demonstrated in patients with chronic liver/biliary failure where an inability to excrete manganese via the biliary system causes increased serum levels, and in patients on total parenteral nutrition (TPN), occupational/inhalational exposure, or other source of excess exogenous manganese. Manganese has been well described in the literature to deposit selectively in the globi pallidi and to induce focal neurotoxicity. We present a case of a 53-year-old woman who presented for a brain MR 3 weeks after liver transplant due to progressively decreasing level of consciousness. The patient had severe liver failure by liver function tests and bilirubin levels, and had also been receiving TPN since the transplant. The MR demonstrated symmetric hyperintensity on T1-weighted images in the globi pallidi. Apparent diffusion coefficient (ADC) map indicated restricted diffusion in the globi pallidi bilaterally. The patient eventually succumbed to systemic aspergillosis 3 days after the MR. The serum manganese level was 195 mcg/l (micrograms per liter) on post-mortem exam (over 20 times the upper limits of normal). The patient was presumed to have suffered from manganese neurotoxicity since elevated serum manganese levels have been shown in the literature to correlate with hyperintensity on T1-weighted images, neurotoxicity symptoms, and focal concentration of manganese in the globi pallidi. Neuropathologic sectioning of the globi pallidi at autopsy was also consistent with manganese neurotoxicity.

Keywords Manganese neurotoxicity · Restricted diffusion · Globi pallidi

Introduction

While it is not currently known why the pallidum is selectively vulnerable to manganese deposition, such deposition has been previously shown in the literature to demonstrate hyperintensity on T1-weighted images due to paramagnetic effects (although not necessarily representing neurotoxicity). Elevated serum manganese levels have been shown to correlate well with the presence of neurotoxicity, and with increased signal intensity in the globus pallidus on T1-weighted MR images. The elevated serum manganese levels, imaging appearance, and pathologic changes on autopsies have all been described in the literature to correspond with high pallidal concentrations of manganese, and to be consistent with nerve cell death. In this case report we present a case of manganese neurotoxocity with symmetric hyperintensity in globi pallidi bilaterally on diffusion-weighted images (DWI) and restricted diffusion on apparent diffusion coefficient (ADC) maps.

Case report

A 53-year-old woman with a history of porphyria presented approximately 3 weeks after her second liver transplant. Her liver function tests were extremely elevated, and she was immune suppressed for transplant purposes. The patient also was on total parenteral nutrition (TPN) for the 3 weeks prior to presentation (at one-third the adult trace element concentration) and intermittently received tube feeds. The patient experienced a progressive decrease in mental status and responsiveness over the 3 weeks after her liver transplant with a low-grade fever and abnormal chest film, so a brain MRI was requested to evaluate for infectious etiology or cyclosporin neurotoxicity. The patient had remained intubated and sedated from the time of surgery to the time of MRI, so neurologic examination was limited at the time and only revealed hypotonia of all extremities with minimal ability to cooperate with commands.

The MRI demonstrated bilateral hyperintensity in the globi pallidi on T2-weighted images and fluid-attenuated inversion recovery images and mild increased signal on T1-weighted images (Figs. 1a,b).

The small focus of decreased signal on T1-weighted images within the right thalamus had minimal peripheral enhancement, which was considered to possibly represent a focus of cerebritis without discrete abscess, especially given the progressive pulmonary opacities that were suggestive of an infectious process.

The ADC values within the globi pallidi were decreased (0.57×10^{-3} mm^2/s on the right and 0.55×10^{-3} mm^2/s on the left) (Fig. 1c,d). We note that the ADC is 0.87×10^{-3} mm^2/s within the normal-appearing putamina, 0.84×10^{-3} mm^2/s in the caudate, 0.86×10^{-3} mm^2/s in the deep frontal periventricular white matter, and 0.75×10^{-3} mm^2/s in the left thalamus in this patient.

The possibility of manganese neurotoxicity was considered at this point; however, the patient succumbed to systemic aspergillosis (confirmed on autopsy) 26 days after transplant with pulmonary involvement and hepatic infarctions. On autopsy, neuropathology showed vacuolar change, presence of macrophages, gliosis, and neuronal loss in the pars interna of the globus pallidus (Fig. 2). It also showed similar vacuolar change in the pars reticulata of the substantia nigra, and per the neuropathologist, these combined findings were very specific for manganese neurotoxicity. Other

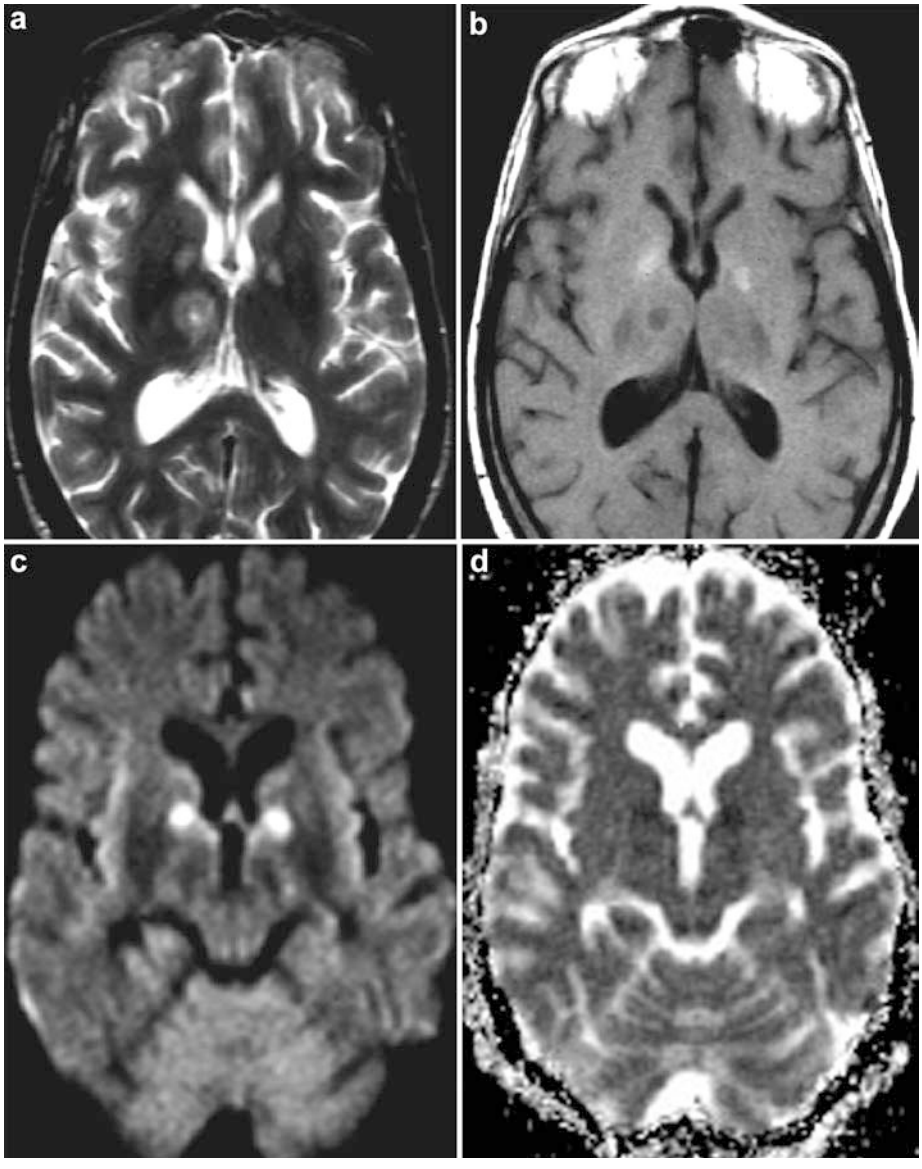

Fig. 1a–d Brain MR in a 53-year-old woman who was 3 weeks status post-liver transplant with elevated liver function tests and immunosuppression presents with progressive decrease in mental status after transplant surgery. **a** Axial T2-weighted image demonstrates bilateral symmetric hyperintensity in the globi pallidi. **b** Axial T1-weighted image illustrates symmetric hyperintensity in the globi pallidi consistent with manganese deposition given the history of liver failure and TPN administration. There is also a hypointensity in the right thalamus. **c** Axial diffusion-weighted (DW) image. There is symmetric hyperintensity in the globi pallidi in the same region of abnormality on the T2-weighted image. Note that the DW/echoplanar images are obtained at a more oblique angle than the other sequences to avoid inclusion of air from the sphenoid sinus (which can produce undesirable artifact). **d** The apparent diffusion coefficient map indicates restricted diffusion (mild hypointensity) in the globi pallidi bilaterally

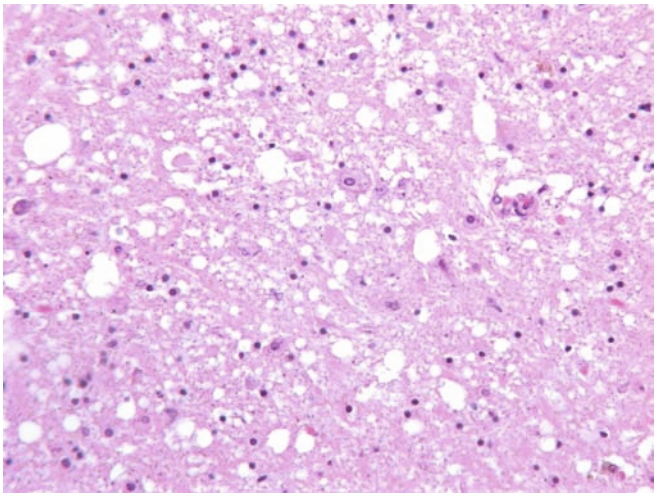

Fig. 2 Histologic sample from the patient's globus pallidus showing vacuolar change, macrophages, gliosis, and neuronal loss (magnification, ×25). Per the neuropathologist, the findings on pathologic section were very specific for manganese neurotoxicity

pathology, such as infection, hemorrhage, or abnormal discoloration, was not noted in the globus pallidus or the substantia nigra. The lesion in the right thalamus was confirmed to be "acute fungal cerebritis." Tissue manganese concentration in the globi pallidi was not measured since testing of that manner was not available within the facilities of our hospital or in other regional institutions. The serum manganese at autopsy was 195 mcg/l (normal is < 8 mcg/l). Total bilirubin 1 day prior to demise was very elevated at 22.9 mg/dl (milligrams per deciliter), and the patient's bilirubin ranged variably from 11.1 to 27 mg/dl over the 3 weeks between transplant and demise.

Discussion

Manganese is an essential trace element in the normal human diet, which is absorbed via the gastrointestinal tract and eliminated primarily via the bile [1]. Serum and brain levels of manganese have been shown to elevate significantly in the setting of liver failure or biliary dysfunction, as demonstrated in rats that became cirrhotic by bile duct occlusion and underwent simultaneous manganese ingestion [2]. A variety of methods have been applied to measure or approximate the patient's exposure to manganese including: serum manganese level [3, 4, 5, 6, 7, 8]; analysis of manganese level in hair [9]; local pallidal measurement of NMR T1 proton relaxation times (done in live rats) [10]; and atomic absorption spectrometry [8, 10]. Patients with chronically elevated serum manganese may be asymptomatic, or may demonstrate a spectrum of symptoms ranging from early/subjective symptoms (such as headache or fatigue), mid-spectrum symptoms (akinetic, rigid, and Parkinson-like), or late/irreversible neurologic sequela (including dystonia); occasionally, cranial nerve palsies or ataxia may result [11]. The Parkinson-like effects in the mid-disease have been hypothesized to be similar to the mechanism of MPTP (1-methyl-4-phenylpyridinium ion, a dopaminergic neurotoxin) in that manganese inhibits aerobic glycolysis in the rat striatum [12]. The mainstay of treatment consists of withdrawal of the offending agent/exposure in the earlier phases of the disease. EDTA chelation has shown variable results and Parkinson medications, such as Levodopa, have not demonstrated any benefit [13, 14, 15]. To our knowledge, no surgical interventions (such as pallidotomy utilized in Parkinson's disease) have yet been performed. Neurotoxicity symptoms and abnormal signal on T1-weighted MR images have been shown to reduce or resolve with withdrawal of the exposure in the earlier stages of the disease and may occasionally resolve in long-term exposure [4, 5, 6].

Manganese neurotoxicity symptoms have previously been shown to correlate with high serum manganese levels (such as seen in our patient), and serum manganese levels have been shown to correlate with concentration of manganese in the globi pallidi [3, 4, 5, 6, 7, 8]. It is currently unknown why manganese selectively accumulates in the globi pallidi. It is thought that manganese may trigger apoptotic-like neuronal cell death secondary to mitochondrial dysfunction in dopaminergic striatal neurons, demonstrated in brains of rats [16, 17]. In previous cases, pathologic sectioning of globi pallidi with high signal intensity on T1-weighted images and high concentrations of manganese has shown atrophy, necrosis, and gliosis consistent with nerve cell death [18]. Our patient had similar neuropathologic findings on autopsy. Patients with liver failure, patients receiving intravenous total parenteral nutrition (TPN), or people in situations of occupational exposure may experience manganese neurotoxicity [19, 20]. The symptoms and neuropathologic appearance in reported cases of manganese toxicity are similar in all of these scenarios [18, 19].

Studies have shown that high signal intensity in the globus pallidus on T1-weighted MR images correlates to blood manganese levels in cirrhotic patients [19, 21], in patients receiving TPN [22, 23], and in cases of occupational exposure [19]. Furthermore, several studies have shown that there is no correlation between the high signal intensity and either portal systemic encephalopathy [24], ammonia levels [24], bilirubin levels [21], or alkaline phosphatase levels [21]. There are other previous studies that have shown correlation between this high signal intensity on T1-weighted images and either bilirubin or ammonia levels in adults with cirrhosis, but these studies did not mention measurement of manganese levels [25, 26]. In these adult cases, the increased signal intensity is likely a result of increased serum manganese (as opposed to bilirubin or ammonia) since manganese is a known paramagnetic substance, and has been shown (on measurements of tissue concentration from pathologic sectioning) to cause increased signal

intensity in the globi pallidi on T1-weighted MR images [18]; hence, increased bilirubin and ammonia levels may be coexistent markers of the hypermanganesemia (in adult cirrhotic patients) since manganese is excreted via the biliary system [18, 19]. We postulate that our patient's elevated bilirubin level was coexistent with her elevated serum manganese level, and the hypermanganesemia was the likely cause of the increased signal intensity in the globus pallidus. This is consistent with the pathologic findings on autopsy, which were specific for manganese neurotoxicity in that location.

Manganese accumulates within mitochondria [27] preferentially via a uniporter mechanism that manganese shares with calcium [28]; however, manganese is slowly transported out of mitochondria via the sodium-independent (and energy-dependent) efflux mechanism. Manganese in the form of Mn^{2+} appears to inhibit both Na(+)-dependent and Na(+)-independent Ca2+ efflux, whereas Ca^{2+} does not appear to inhibit Mn^{2+} efflux from brain mitochondria [28]. Mn^{2+} inhibition of Ca^{2+} efflux is thought to increase the probability of the mitochondria undergoing mitochondrial permeability transition (in which the mitochondria swell and relatively large pores in the membrane open to allow release of substances) as well as decrease oxidative phosphorylation [28, 29]; hence, cellular energy is depleted since decreased oxidative phosphorylation causes decreased ATP synthesis [29, 30]. We postulate that given the demonstrated mechanism of manganese neurotoxicity mentioned above, the decrease in ATP synthesis may have caused dysfunction of the Na+–K+ATPase enzyme on the membrane of neurons. Previous literature has suggested that in the setting of cerebral ischemia, the hyperintense signal abnormality on DWI images is the dysfunction of Na–K ATPase enzyme causing accumulation of sodium and water inside the cell and hence cytotoxic edema [31]. This cytotoxic edema and cell death causes restricted motion of protons, which is seen as bright signal on DWI [32, 33, 34]. In theory, the dysfunction of oxidative phosphorylation (secondary to manganese toxicity) may have decreased ATP synthesis and caused dysfunction of Na+–K+ATPase enzyme, resulting in the restricted diffusion (and hence cytotoxic edema) within the globi pallidi in our patient.

Our patient deteriorated rapidly and expired over a period of 3–4 weeks after surgery, with progressively decreasing mental status and worsening hypotonia over that time. The exact age of the lesions in the globus pallidi and the onset of symptoms is unknown since the patient had remained intubated and sedated after transplant. Also, the patient suffered from systemic aspergillosis, which likely affected her mental/neurologic status as well; therefore, it is difficult to determine which clinical symptoms were related solely to manganese toxicity in this case.

Conclusion

In conclusion, our patient's serum manganese level (over 20 times the upper limit of normal) and neuropathologic findings were very specific for manganese neurotoxicity. Although the patient eventually succumbed to systemic aspergillosis, we believe the patient concomitantly suffered from acute or subacute manganese neurotoxicity. Since manganese has been previously demonstrated as a cause of focal neurotoxicity in the globi pallidi, we postulate that in our patient, the selective accumulation of manganese (due to severe liver failure and TPN) induced such focal neurotoxicity, which caused the symmetric diffusion abnormality in the globi pallidi.

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