Brain iron accumulation in a blood donor family with restless legs syndrome

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Introduction. The pathophysiology of restless legs syndrome (RLS) is complex. Secondary RLS with iron deficiency –which suggests disturbed iron homeostasis– remains to be elucidated.

Case reports. We report the findings from a unique blood donor family with RLS. Three blood donors family members were diagnosed with RLS defined by the International RLS Study Group and without history of neurologic diseases and RLS symptoms in the last 3-5 years (range of blood donation: 10-40 years). The neurological examination and electromyographies were normal. A polisomnography showed disturbed nocturnal sleep with a reduction in sleep efficiency and an increased periodic limbs movement index. The cranial MRI showed brain iron deposits in basal ganglia, substantia nigra, red nuclei and dentate nuclei. Phenotypic and genotypic studies rule out genetic haemochromatosis or iron overload.

Conclusion. The abnormal iron accumulation in the basal ganglia indicated a complex iron metabolism disorder of the central nervous system. Further studies are warranted to confirm our findings and its role in the pathophysiology of RLS.

Key words. Basal ganglia. Blood donors. Brain iron deposits. Periodic leg movements. Restless legs syndrome.

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Introduction

Restless legs syndrome (RLS) is a neurological condition with a complex pathophysiology. How these etiological factors: dopaminergic dysfunction, impaired iron homeostasis and genetic disposition, are interrelated in the genesis of RLS remains unclear.

Brain image and autopsy studies have shown brain iron deficiency in the substantia nigra [1,2], or other structures as thalamus and dentate nuclei [3]. Nevertheless the literature show some discrepancies, as some studies do not find any difference in the iron content of several structures (substantia nigra, globus pallidus, caudate, thalamus) [4], and others even find an increased iron content in globus pallidus and substantia nigra [5]. There have been reported RLS in patients with high serum ferritin secondary to hemochromatosis [6], in dysmetabolic iron overload syndrome [7], and in other medical conditions.

RLS treatment guidelines recommend iron when peripheral iron level is low. Intravenous iron treatment may achieve considerably higher peripheral brain iron level than oral iron treatment, and may be more effective, because of the central role for brain iron levels in RLS pathogenesis [8].

The aim is to report the unusual neuroradiological findings of three members from a unique regular blood donor family with RLS.

Case reports

We studied three family members: the 74-year-old father, his daughter and son aged 45 and 39 years old respectively (Fig. 1). They were referred to the Sleep Unit by leg dysesthesias, urgency to move them, which worsen at rest and night, and were relieved by movement. The symptoms started at around 30 years old in the father and the son, and at 44 years in the daughter. All of them met RLS diagnostic criteria defined by the International Restless Legs Study Group in 2014. Regarding their medical history, the father was a smoker, and suffered a sensitive lacunar stroke at 73 years old. The daughter was a smoker and suffered vitamin B_{12} deficiency secondary to a chronic atrophic gastritis, and vitamin D deficiency. The son was a smoker, obese, and suffered hypertension and dyslipidemia. They were regular blood donors, the father for 40 years, with a frequency of 4 donations/year; the daughter for 12 years, with 1 donation/year, and the son for 20 years, with 2-4 donations/year.

After signing an informed consent, neurological examination, EMGs, polysomnography, laboratory evaluation (serum iron, ferritin, transferrin, transferrin saturation and soluble receptor, haemoglobin); and a genetic study for haemochromatosis mutations, and other neurodegeneration diseases

Table. Polysomnography and iron parameter data.

	Total sleep time	WASO	Sleep latency (min)	REM latency (min)	No REM (%)	REM (%)	Sleep efficiency	PLM/h	AHI/h	Hemoglobin (mg/dL)	Ferritin (μg/L)	Transferrin (mg/dL)	Transferrin saturation (%)	Vitamin B_{12} (ng/mL)
A	208	10	75	–	100	0	52.2	97.6	23.1	9.4	6	410	1.9	327
B										16.3	55	219	38	148
C	390	59	6	193	83.6	16.4	86.8	22.2	11.2	15.5	170	269	35	305

AHI: apnea hypopnea index; PLM: periodic leg movements; WASO: wake after sleep onset.

with brain iron accumulation were performed. We performed a 1.5 T brain MRI to all of them to complete the study

Neurological examination was normal and EMGs recordings were normal without peripheral neuropathy. We excluded secondary RLS and mimics in all cases.

Laboratory tests revealed iron deficiency anemia in the father, and vitamin B_{12} deficiency without anemia in the daughter (Table).

A polysomnography in the father and the son, showed fragmented sleep with a reduction in total sleep time, low sleep efficiency, and an increase in PLMs index. The father showed a moderate sleep apnea syndrome, and the son a mild sleep apnea syndrome, related to his obesity. The daughter refused the PSG.

Genetic studies ruled out the presence of *HFE* mutations responsible of haemochromatosis, as well as other medical conditions related with brain iron overload such as: transferrin receptor (*TFR2* gene), ferroportine (*SLC4* gene) and neuroferritinopathy (*FTL* gene).

Cranial MRIs (written inform consents provided) showed an abnormal hipointensity in the caudate nuclei, lenticular nuclei, dentate nuclei, substantia nigra pars compacta, and red nuclei, suggesting an increase of ferromagnetic content in these structures (Fig. 2).

Discussion

Eckbom, in his first description of RLS, noticed the relation between iron metabolism and RLS, with an increased incidence of RLS in patients with iron deficiency anemia. Since 2001 anatomopathological and radiological studies suggest the presence of a disturbance in the iron content in basal ganglia, substantia nigra, and other brain structures in RLS patients.

Beyond the discrepancies in the literature regarding the presence or not of brain iron deficiency in RLS patients [1-5], several studies found increased ferritin and reduced transferrin concentration in cerebrospinal fluid of RLS patients compared to control subjects, with no differences in their serum levels [9]. This finding, together with the decreased transferrin receptor expression in the brain microvasculature of RLS patients, suggests a reduced iron transport across the blood-brain barrier. The possibility that the cause for the altered brain iron acquisition in RLS lies within the cells, perhaps in the neuron themselves, has been raised previously [10]. An anatomopathological study found an increased number of mitochondria, and increased mitochondrial ferritin, in substantia nigra of RLS patients versus controls [11]. According to this hypothesis, our unusual finding of increased iron content in substantia nigra, with normal or low peripheral iron, would suggest a more complex brain iron acquisition disturbance. Iron would pass the blood-brain barrier and reach the neurons of basal ganglia and substantia nigra, so the disturbance would be present at the molecular level.

Hepcidin has recently become a subject of interest for researchers in RLS. Is a protein hormone with a crucial role in iron homeostasis. According to this hypothesis our patients could manifest a low brain hepcidin expression due to downregulation, since brain iron overload have been shown to reduce hepcidin expression in the brain, such as inflammation and hypoxia [12]. In any case, little is known about the molecular mediator of local hepcidin expression in the brain.

Our study is limited by the lack of data of cerebrospinal fluid iron parameters, as this technique is not available in our center. A 3 T MRI would allow quantifying the brain iron content in several structures, but unfortunately it is not available in our center. Further studies are needed to confirm our find-

Figure 1. Genealogical tree. A: 74 years old father; B: 45 years old daughter; C: 39 years old son.

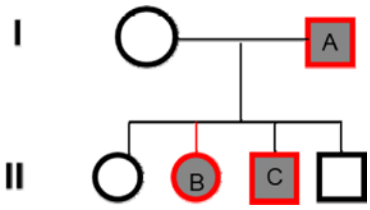
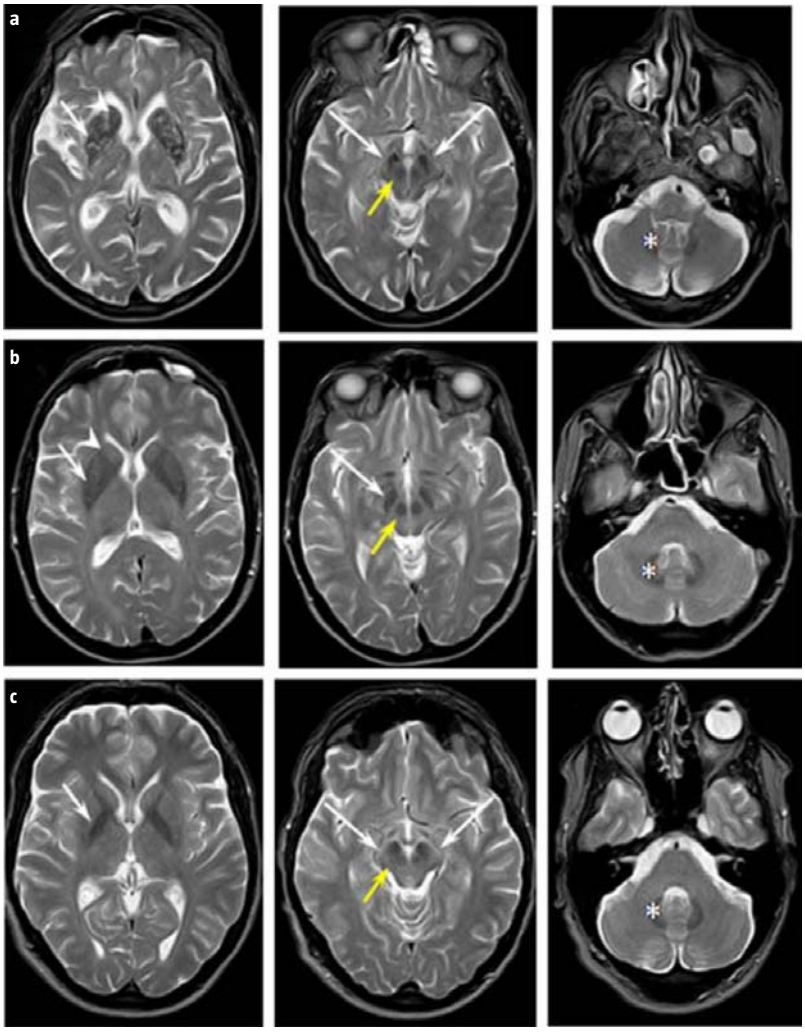


Figure 2. Axial SE T_2W MR images of the father (a), the daughter (b) and the son (c). Showed hypointensity in caudate nuclei (head arrows), lenticular nuclei (short white arrows), dentate nuclei (asterisks), substantia nigra pars compacta (long white arrows) and red nuclei (yellow arrows) suggesting an increase of ferromagnetic deposits.



ings and study the role of increased brain iron content in some RLS patients.

We suggest performing a brain MRI to quantify the brain iron content in RLS patients. It should be mandatory before an iron intravenous treatment is proposed, as there could be some RLS patients with increased brain iron content, but normal or low serum iron levels, and this treatment could be harmful. Further studies should investigate this hypothesis.

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Aumento de los depósitos cerebrales de hierro en una familia de donantes de sangre con síndrome de piernas inquietas

Introducción. La fisiopatología del síndrome de piernas inquietas (SPI) es compleja. El mecanismo a través del cual la ferropenia favorece el desarrollo del SPI no está esclarecido, aunque se sugiere la presencia de una alteración en la homeostasis cerebral del hierro.

Casos clínicos. Se presentan los hallazgos inusuales en una familia de donantes de sangre con SPI. Tres miembros de la misma familia fueron diagnosticados de SPI, cumpliendo los criterios definidos por el grupo internacional para el estudio del SPI (*International Restless Legs Syndrome Study Group*). Todos eran donantes de sangre habituales (rango de donación: 10-40 años) y los síntomas de SPI tenían un curso de 3-5 años. La exploración general y neurológica fue normal en todos los casos, así como los electromiogramas. El estudio fenotípico y genotípico descartó la presencia de hemocromatosis y otras causas genéticas de sobrecarga cerebral de hierro. Los estudios polisomnográficos mostraron sueño nocturno perturbado, con reducción de su eficiencia, y un aumento del índice de movimientos periódicos de las piernas. La resonancia magnética craneal evidenció un aumento de los depósitos cerebrales de hierro en los ganglios basales, la sustancia negra, el núcleo rojo y los dentados.

Conclusión. Este aumento patológico de los depósitos cerebrales de hierro sugiere la presencia de un complejo trastorno del metabolismo cerebral del hierro en nuestros pacientes. Futuros estudios deben confirmar estos hallazgos y profundizar en el estudio de su relación con la fisiopatología del SPI.

Palabras clave. Depósitos cerebrales de hierro. Donantes de sangre. Ganglios basales. Metabolismo del hierro. Síndrome de piernas inquietas.