EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2020,15 (26) 107–109
(*FORMERLY: CAPSULA EBURNEA*)

Case report

BRAIN IRON ACCUMULATION: DON'T FORGET ACERULOPLASMINEMIA!

Paola Feraco [1,2], Alberto Conficoni [3], Benedetto Petralia [1], Pierluigi Lanza [4]

1. Department of Neuroradiology, Ospedale S. Chiara, Azienda Provinciale per i Servizi Sanitari, Trento, Italy
2. Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy
3. Neuroradiology Unit, Department of Radiology, Azienda Ospedaliero-Universitaria di Ferrara, Italy
4. National Research Council, institute for Biomedical Research and Innovation IRIB, Mangone (CS), Italy

ARTICLE INFO

Article history:
Received 27 May 2020
Revised 15 June 2020
Accepted 01 July 2020

Keywords:
Aceruloplasminemia (Ceruloplasmin deficiency), iron metabolism disorders, neurodegeneration with brain iron accumulations, NBIA, Neurodegenerative Diseases, Magnetic Resonance Imaging, MRI.

ABSTRACT

Aceruloplasminemia is a rare autosomal recessive disease, affecting iron metabolism, with typical onset in adulthood. It is brought about by mutations in the ceruloplasmin gene. Laboratory investigations reveal microcytic anemia, elevated serum ferritin, and a complete absence of serum ceruloplasmin ferroxidase activity. Clinical manifestations reflect the specific locations of neurodegeneration and iron deposition. Neuroradiological findings, characterized by symmetric "blooming" hypointense deposits on T2-weighted and T2*-weighted sequences in the basal ganglia, thalamus and cerebellum (especially dentate nucleus), are an exclusive feature of aceruloplasminemia. We report a case of a 52-year-old man who underwent MR exam to further characterize a diagnosis of AP which showed typical iron deposition and unusual T2-weighted/FLAIR hypointensities in the subcortical white matter U fibers, suggesting that brain iron accumulation can be more extensive than previously believed.

1. Introduction

Aceruloplasminemia (AP) is a rare autosomal recessive disease, affecting iron metabolism, with typical onset in adulthood. It is determined by mutations of the ceruloplasmin (CP) gene, absence of serum CP, low serum iron levels and iron accumulation in the liver, brain and other organs[1]. Clinical manifestations reflect the specific sites of neurodegeneration and iron deposition. Magnetic resonance imaging (MRI) usually shows symmetric "blooming" hypointense deposits on T2-weighted and T2*-weighted sequences in the basal ganglia, thalamus and cerebellum which are an exclusive feature of AP. This widespread pattern of involvement helps distinguish AP from other types of neurodegeneration involving brain iron accumulations. We report a case of a 52-year-old man who underwent an MR exam to further characterize a diagnosis of AP which showed typical iron deposition and unusual T2-weighted/FLAIR hypointensities in the subcortical white matter U fibers, suggesting that brain iron accumulation can be more extensive than previously believed.

2. Case report

A 52-year-old Caucasian man, with a ten year history of type 2 diabetes mellitus, came to our attention for progressive cognitive deterioration and growing irritability over the previous two years. Neurological examination showed moderate mixed symmetric tremor of the upper limbs, with a mini-mental test examination score of 24 (normal range 24-30) and irritability.

Liver function was within the normal range. An ophthalmological consultation showed signs of retinal degeneration, but no Kayser-Fleischer rings. He had also mild microcytic anemia (hemoglobin level, 10,4 g/dL; mean corpuscular volume, 78 fl), with ferritinemia above 1,500 ng/mL. Urinary and serum copper levels were undetectable. Moreover, serum CP levels were undetectable, thus AP was suspected. To further characterize the clinical diagnosis, the patient underwent brain MRI examination (3T GE Discovery MR750 scanner; 8-channels head coil). T2-weighted fluid attenuated inversion recovery (FLAIR) and T2*-weighted gradient recalled-echo (GRE) pulse sequences revealed an hypointense signal in several deep gray matter structures:

* *Corresponding author*: Paola Feraco *paolaferaco@apss.tn.it;*
DOI: 10.3269/1970-5492.2020.15.26
 ISSN: 2279-7165 - Available on-line at www.embj.org

putamina, dentate nuclei, substantia nigra, red nuclei, inferior and superior colliculi and thalamic nuclei (pulvinar in particular) (Figure 1). Diffuse hypointensities related to iron deposition were also present on GRE images in the subcortical white matter U fibers. Moreover, the imaging protocol was completed with a T2* multi-echo sequence which allows Iron quantification. The images confirmed the iron overload (Figure 2). Considering the typical MRI brain iron deposition pattern the neuroradiological diagnosis was consistent with the clinical data. The patient underwent treatment with iron chelators with progressive reduction of ferritinemia without significant clinical benefit to neurological symptoms.

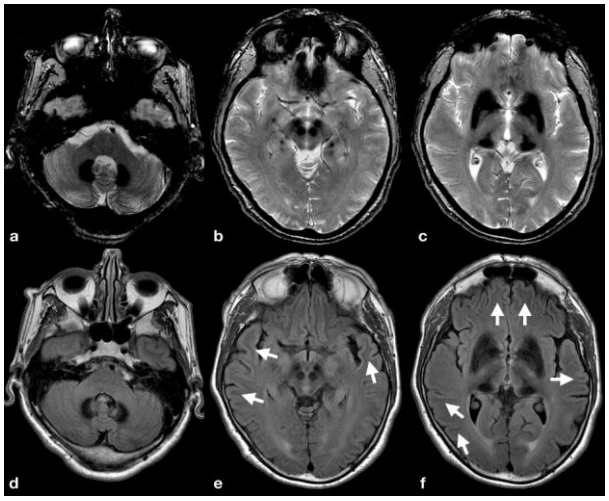

Figure 1. T2-weighted GRE (top row) and FLAIR (bottom row) sequences passing through the middle cerebellar peduncles (a, d), midbrain/diencephalon (b, e) and the basal ganglia region (c, f). Iron deposits are appreciable as "blooming" hypointensity areas bilaterally in the dentate nucleus (a,d), red nucles and substantia nigra (b, e), basal ganglia and thalami (c, f). Subcortical white matter ("U" fibers) involvement is well demonstrated in FLAIR imaging (arrow in e and f).

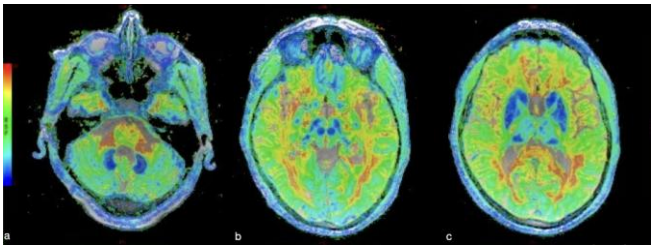

Figure 2. Color coded T2* map images (blue: high iron deposits; red: no iron deposits) showing the iron overload in dentate nucleus (arrow in a), red nucleus and substantia nigra (open circle in b), caudate nucleus, pallidus and putamen of both sides (c). The involvement of the thalami is also evident due to major deposits into the pulvinar (arrow in c).

3. Discussion

AP is a rare autosomal recessive disease, affecting iron metabolism, with typical onset in adulthood. It is determined by mutations of the CP gene (located on the long arm of chromosome 3), absence of serum CP, low serum iron levels and iron accumulation in the liver, brain and other organs, with a rare prevalence (1 case/2 million people) [1].

CP plays an antioxidant role by transforming iron from its Fe^{2+} to Fe^{3+} state, thus preventing oxidative damage caused by the formation of free radicals Fe^{2+} by the Fenton reaction. Furthermore, by oxidizing iron from Fe^{2+} to Fe^{3}, CP allows the escape of iron from the cell since only ferric iron can be absorbed by transferrin in the bloodstream [2].

Iron accumulates in the liver, pancreas, retina and brain. Clinical manifestations reflect the specific sites of neurodegeneration and iron deposition, these include: diabetes mellitus, retinal pigmentary degeneration, dystonia, extrapyramidal signs, cerebellar ataxia, and dementia. Diabetes usually develops after the age of 30, while neurological symptoms usually develop after the age of 50 [3]. A diagnosis of aceruloplasminemia is made based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation and a variety of tests. The limitation of our case is represented by the lack of a genetic diagnostic test. Indeed, although the definitive diagnostic test is to demonstrate the mutations in the CP gene, undetectable CP, microcytic anemia, hyperferritinemia, and low copper levels together with clinical symptoms, as in our case ,are usually enough to make a diagnosis of AP.

Moreover, the typical brain iron deposit patterns, easily detected using MRI, may be useful to direct the diagnosis in poorly symptomatic or accidental cases. Indeed, “blooming” hypointense deposits on T2-weighted and T2*-weighted pulse sequences in the basal ganglia, thalamus and cerebellum (especially dentate nucleus) are an exclusive feature of AP.

Neuroradiological findings allow for a differential diagnosis to be made easily in the field of neurodegeneration with brain iron accumulations (NBIA) with adult onset, characterized by brain iron deposition and associated with neuronal death. In these conditions iron deposition is either more limited (e.g. confined to the pallidus) or associated with other features (e.g. cavitation, cerebellar atrophy or thin corpus callosum) [4]. As in our case, the widespread pattern of involvement helps distinguish AP from other NBIA. Moreover, considering the high magnetic field used (3T), we detected T2-weighted FLAIR hypointensities in the subcortical white matter U fibers too, suggesting that brain iron accumulation in AP is more extensive than previously believed and not only confined into the basal ganglia and thalami. This finding, could be related to the long course of the disease. Indeed, iron deposition usually increases over time. This particular finding, thanks to the use of susceptibility weighted imaging (SWI) sequences, has been described only recently in an isolated case together with cortical and subcortical gray matter iron deposition and has not been related to other iron overload diseases yet [5].

However, although brain iron overload and neurological symptoms are late manifestations of ACP patients, some reports described affected patients without or with very mild brain iron overload [6]. Lastly, using advanced MRI techniques, such as multi-echo T2* weighted sequences, to quantify iron overload could be useful in a patient’s treatment follow-up with iron-chelators.

4. Conclusion

Undetectable CP, microcytic anemia, hyperferritinemia, and low copper levels together with clinical symptoms are usually enough to diagnose AP. On the other hand, the typical brain iron deposits patterns at MRI, may be useful to direct the diagnosis in poorly symptomatic or accidental cases. Since these deposits are well demonstrated by using T2*-weighted or the more recently introduced SWI [7], including these pulse sequences in daily diagnostic protocols is becoming increasingly important especially in consideration of the significant spread of high- and very-high field strength MRI scanners. These characteristic neuroradiological findings together with clinical features and family history should guide investigation with genetic testing.

References

1. Nittis T, Gitlin JD. The copper-iron connection: hereditary aceruloplasminemia.Semin Hematol. 2002 Oct; (39) 282-289.
2. Kono S. Aceruloplasminemia: an update. Int Rev Neurobiol. 2013; (110): 125-51.
3. McNeill A, Pandolfo M, Kuhn J, Shang H, Miyajima H. The neurological presentation of ceruloplasmin gene mutations.Eur Neurol. 2008 Jul; (60):200-205.
4. Salomão RP, Pedroso JL, Gama MT, Dutra LA, Maciel RH, Godeiro-Junior C, Chien HF, Teive HA, Cardoso F, Barsottini OG.A diagnostic approach for neurodegeneration with brain iron accumulation: clinical features, genetics and brain imaging. Arq Neuropsiquiatr. 2016Jul; (74):587-596.
5. Zhou L, Chen Y, Li Y, Gharabaghi S, Chen Y, Sethi SK, Wu Y, Haacke EM. Intracranial iron distribution and quantification in aceruloplasminemia: A case study.Magn Reson Imaging. 2020 Feb; 70:29-35
6. Pelucchi S, Mariani R, Ravasi G, Pelloni I, Marano M, Tremolizzo L, Alessio M, Piperno A. Phenotypic heterogeneity in seven Italian cases of aceruloplasminemia. Parkinsonism Relat Disord. 2018 Jun (51):36-42.
7. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YC. Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. AJNR Am J Neuroradiol. 2009 (30):19-30.