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Neurodegeneration with brain iron accumulation (NBIA) encompasses a heterogeneous group of rare diseases characterized by abnormal progressive iron accumulation in the basal ganglia (BG), movement disorders, and cognitive disability.[1] β propeller protein-associated neurodegeneration (BPAN) is, to date, the most common NBIA disorder.[2] It is caused by mutations in an X-linked gene, *WDR45,* which has an important role in autophagy.[3-5] The disease is more common in females and typically presents with global developmental delay, speech impairment, abnormal gate, sleep disturbances, and epilepsy in childhood followed by severe dystonia, parkinsonism, and progressive dementia in young adulthood, though the phenotypic spectrum is broader and includes Rett syndrome, developmental and epileptic encephalopathy, and intellectual disability.[6-8] The distinctive BPAN neuroradiologic findings are well-known in adolescence and adulthood and include the following: T2, T2*, and SWI hypointensity in the substantia nigra (SN) and GP; the "halo sign" on T1WI (ie, a symmetric hyperintense signal surrounding a thin, dark, central band in the SN and cerebral peduncles), which is pathognomonic for BPAN; a normal or thinned corpus callosum; and mild-to-moderate global cerebellar and cerebral atrophy.[5,6,9,10] Findings of neuroimaging performed during early childhood are nearly all normal. In some cases, delayed myelination, nonspecific cerebellar and cerebral atrophy, and a thin corpus callosum have been described.[2,11] Because the clinical features are not specific and imaging may not demonstrate the classic findings at a young age, the diagnosis is often made with gene panel or exome sequencing, which reveals a mutation in *WDR45.*[7]

The article by Papandreou et al,[12] published in the current issue of the *American Journal of Neuroradiology*, represents an important retrospective cohort study of 15 pediatric patients with a confirmed pathogenetic *WDR45* variant, focusing on early MR imaging features. The authors took into account a vast amount of neuroimaging findings and reported that early neuroradiologic features, in most cases, included dentate nuclei hyperintensity, GP and SN swelling and hyperintensity, as well as a thin corpus callosum and cerebral and cerebellar atrophy of various degrees. They also observed optic nerve thinning and an unusually small midbrain. Iron deposition was uncommon in patients younger than 4 years of age and was never present in children younger than 3 years of age but was evident in almost all patients scanned at 5 years of age or older.

A minor criticism of the present work[12] was that the assessment of cerebral volume reduction, detected in most of the cases, was subjective and is actually unreliable due to lack of age-matched controls. Indeed, in children, subjective assessment of brain atrophy can be difficult because of craniocerebral disproportion. Furthermore, the authors report midbrain atrophy in all cases, whereas no obvious midbrain atrophy is observed in Fig 1 and, in general, in any of the other cases reported.[13-16] Another critical issue concerns the assessment of optic nerve atrophy in axial sections, which we do not consider correct because in general, errors occur when measuring optic nerve diameter on axial images.

If one focuses on the GP and SN and on the iron-sensitive sequences (T2WI, T2*WI, and SWI), the most relevant evidence is that iron deposition is not present early in the course of the disease but accumulates with time. In particular, there is some sort of evolution of signal abnormalities in these structures from early childhood to early adulthood that could be considered highly specific for BPAN and that is represented by an early, enlarged GP and SN appearance, with slight T2 hyperintenisty and subsequent progressive iron accumulation. SWI sequences can detect very early iron deposition. Iron accumulates in the SN, emerging as the most affected nucleus and, to a lesser extent, in the GP. On T2WI or SWI, the SN results are usually more hypointense compared with the GP, a feature that may help distinguish BPAN from other forms of NBIA.[9] Sometimes, on the T1WI the halo sign is evident in the SN.[2,5] This is a late sign, and its absence in the article by Papandreou et al[12] could be related to the young age of their patients (0–18 years of life).

Most interesting, it is not entirely clear why GP and SN enlargement and T2 hyperintensity predominate early. In four of our cases,[15] we interpreted the swelling as a very early inflammation caused by dysfunction in the autophagy-lysosome complex. The authors[12] also noted that similar neuroimaging findings have been reported in cases with biallelic *WIPI2* mutations,[17] which, similar to *WDR45* (also known as *WIP14*), belong to the family of WD-repeat proteins, which have an essential role in the early

stages of autophagy. We agree that it would be interesting to ascertain whether a similar neuroimaging pattern is present in other congenital autophagy disorders. It is certain, however, that neuroinflammation evolves rapidly in neurodegeneration and progressive iron deposition,[18,19] highlighting how the first abnormality is due to cellular damage, while the accumulation of iron is probably only a late epiphenomenon of the degenerative process.[20,21]

Concerning other characteristic imaging signs, in all the cases reported by Papandreou et al[12] and, in general in most of the cases reported in the literature,[13-16] transient or persistently observed T2-hyperintense signal in the dentate nuclei is a typical finding that helps suggest the diagnosis. This is a finding not seen in other NBIA disorders and, from a pathophysiologic point of view, also probably related to chronic inflammatory changes.[12] Delayed myelination is a transient, frequent finding that normalizes during the follow-up MR imaging;[11,14] thin corpus callosum and cerebellar atrophy (present in other NBIA disorders) are prominent features frequently seen in early childhood[11] but are nonspecific signs.

We believe one of the major merits of the present study is stressing the important role of early MR imaging findings to reach an accurate and early BPAN diagnosis for the best multidisciplinary management of these patients. Even though normal brain MR imaging findings do not exclude BPAN in a young child, early neuroimaging markers highlighted by Papandreou et al,[12] such as GP and SN swelling, dentate nuclei T2 hyperintensity, corpus callosum thinning, and cerebral and cerebellar atrophy in the appropriate clinical context, may strongly suggest the diagnosis. In agreement with the authors, we believe that it is important to not discard a variant of *WDR45* in the absence of iron accumulation in the basal ganglia in the early stages of the disease.

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