CASE

13-year diagnostic delay as cerebral palsy of an Iraqi patient with NBIA type 4

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Neurodegeneration with brain iron accumulation (NBIA) comprises a group of heterogeneous genetic disorders characterized by intensive iron precipitation in specific sites of the brain. Diagnosis and classification can be made based on the clinical manifestations, neuroimaging signs, and genetic confirmation.[1]

PRACTICAL IMPLICATIONS

Consider neurodegenerative disorders in the differential diagnosis of cerebral palsy in the presence of progressive pattern of illness and positive family history. Abnormal MRI signals in the basal ganglia may help distinguish NBIA in patients with cerebral palsy.

Case report

A 22-year-old man presented to the neurology clinic in Baghdad Teaching Hospital Medical City Complex, Baghdad, in 2016 because of progressive difficulty in walking. He is the second boy born to parents of consanguineous marriage. He has 1 healthy brother and an 8-year-old female cousin with autistic features and cognitive deficits. The patient's father's cousin had motor disability and mental retardation and died in his 30 s.

The patient was born prematurely by vaginal delivery, with a birth weight of 1500 g, and was admitted to the neonatal intensive care unit for 3 days. His development showed mild motor delay, speech difficulty, and subsequent mild intellectual difficulties. At age 9, he developed tiptoe walking with progressive posturing of legs and feet and was diagnosed with cerebral palsy. Supportive treatment and orthopedic operations were provided. At age 12, he demonstrated cognitive function decline. At age 20, he developed generalized tonic seizures that were controlled by carbamazepine. At that time, MRI of brain was requested and reported normal. On presentation, the examination revealed skeletal deformities, dependent ambulation, dysarthria, intact cranial nerves, and limitation of motor activities due to moderate spasticity/dystonia. The upper limbs showed brisk deep tendon reflexes and positive Hoffmann sign, while the lower limbs showed tendon reflexes that are difficult to elicit and greater weakness. The sensory status could not be assessed due to cognitive impairment. Whole Exome Sequencing was performed in Centogene Lab—a rare disease company in Germany, revealing a pathogenic homozygous variant (c.158 G > A p. [Gly53Glu]) in the C19orf12 gene, which confirmed the diagnosis of NBIA type 4 mitochondrial membrane protein-associated neurodegeneration (MPAN). Thereafter, thorough ophthalmologic examination of the patient revealed optic nerves atrophy, and a new radiologic opinion of the brain MRI confirmed the appearance of iron accumulation in both Globus pallidus and substantia nigra (figure, A–C).

Discussion

Many subtypes of NBIA have been described. Pantothenate kinase-associated neurodegeneration from mutations in PANK2, phospholipase A2-associated neurodegeneration due to mutation in PLA2G6, MPAN caused by mutations in C19orf12, and beta-propeller

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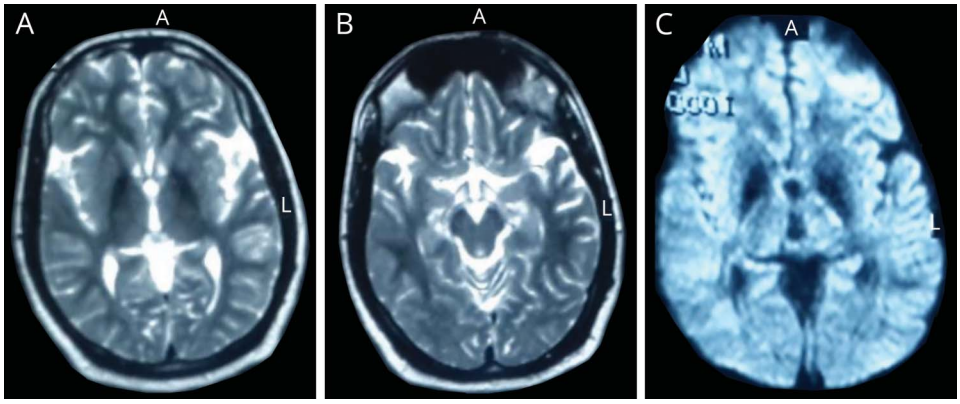
Figure Brain MRI showing iron accumulation in Globus pallidus and substantia nigra



(A–C) MRI of brain, axial T2WI (A and B), DWI (C), 1.5 Tesla, showed homogenous hypointense signal changes, bilateral symmetrical in Globus pallidus (A and C) and substantial nigra (B). DWI = diffusion-weighted image; T2WI = T2-weighted image.

protein-associated neurodegeneration from mutations in WDR45 represent the 4 major subtypes with autosomal recessive inheritance.[2] The onset and progression of NBIA disorders are variable. The typical, but not universal, clinical features are extrapyramidal and may be accompanied by other highly variable manifestations like ataxia, spasticity, bulbar dysfunction, neuropsychological manifestations, ophthalmologic features like optic nerve atrophy and retinal pigmentation, and seizure, which is described as a rare, and late-onset, feature.[1] Most NBIA subtypes display iron precipitation in Globus Pallidus, but each may show other pivotal MRI features that differentiate them from other subtypes.[3]

In this case scenario, cerebral palsy does not fit as it is a group of heterogeneous neurodevelopmental disorders characterized by permanent and static course of illness, disruption of the usual developmental process in early childhood leading to activity limitations. It is nonprogressive, but manifestations are changeable.[4] As a result, the key characteristics that should cast a doubt on the cerebral palsy diagnosis were consanguinity and suspicious family history, neurodevelopmental regression, rigidity (as a prominent feature) on physical examination, and MRI abnormalities confined to the basal ganglia. Lack of careful history taking and clinical reasoning, rarity of the disease, lack of specificity of the symptoms and signs, and lack of awareness in the medical community were the major contributing factors to the misdiagnosis.

This is among the first genetically confirmed cases of MPAN reported in Iraq. A missense variant was detected in the C19orf12 gene, which was not tested in the parents. The nucleotide exchange causes change from glycine (Gly) to glutamic acid (Glu) at position 53 of the C19orf12 protein. This variant is neither listed in HGMD (in several populations for allele frequencies [gnomAD, ESP and 1000 genomes project]) nor listed in PubMed and Google search engines. Different variants affecting the same amino acid residue number 53, which changed Gly to Arginine (Arg), were described by several authors to be disease causing.[5] For this reason, and because it is rare and affects a highly conserved amino acid residue, it is classified as a likely pathogenic variant.

This report highlights the importance of expanding the scope of thinking about rare metabolic/genetic causes of atypical cerebral palsy cases, whose diagnosis is assisted by clinical history and examination, neuroradiologic clues, and molecular genetic investigations, if available.

Author contributions

A.S. Hadi: diagnosis of the case, acquisition of the data, analysis and interpretation of the data and drafting the manuscript. N.W. Saadi: conceptualization of and designing the study, analysis and interpretation of the data and drafting the manuscript for intellectual content. Q.A. Fahad: analysis and interpretation of data.

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