CASE REPORT / CAS CLINIQUES

PANTOTHENATE KINASE ASSOCIATED NEURODEGENERATION: CASE SERIES.

NEURODEGENERESCENCE ASSOCIEE A UN DEFICIT EN PANTOTHENATE KINASE : SERIE DE CAS.

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ABSTRACT

Background:

Neurodegeneration with brain iron accumulation (NBIA) encompasses a heterogeneous group of hereditary disorders characterized by iron deposition particularly in the basal ganglia. Pantothenate kinase-associated neurodegeneration (PKAN) is the most common NBIA. PKAN, due to mutation in the PANK 2 gene has two main presentations.

Case report:

The classic form usually starts in the first decade of life with severe dystonia, dysarthria, parkinsonism, pyramidal, visual signs, and cognitive disturbances with an aggressive course, leading to death by the second decade of life. The atypical form is characterized by a slower progression, and a more benign course. A brain magnetic resonance imaging usually shows the eye of the tiger sign. Here, we report four cases whose age of onset and clinical presentation suggests typical form of PKAN.

Conclusion:

In sum, the data of our patients corroborated those of the classic form of PKAN. The perspective in this entity is the development of rational therapeutics targeting the primary biochemical anomaly, with compounds that bypass the defective PANK2 enzyme including phantasein, phosphopanthethein and coenzyme A.

RESUME

Introduction :

La neurodégénérescence avec accumulation intracérebrale de fer (NBIA) constitue un groupe hétérogène de pathologies héréditaires caractérisées par un dépôt de fer en particulier dans les noyaux gris centraux. La neurodégénérescence associée à un déficit en Pantothenate kinase (PKAN) représente la forme la plus courante de NBIA. Elle est due à une mutation dans le gène PANK 2 et comporte 2 formes cliniques.

Cas cliniques :

La forme classique débute généralement au cours de la première décade par une dystonie sévère, une dysarthrie, un parkinsonisme, des signes pyramidaux, visuels et des troubles cognitifs d'évolution sévère

entrainant la mort au cours de la deuxième décade. La forme atypique est caractérisée par une progression plus lente et une évolution plus bénigne. Une imagerie par résonance magnétique cérébrale montre généralement le signe des yeux de tigre. Nous rapportons ici quatre cas dont l'âge d'apparition et la présentation clinique suggèrent une forme typique de PKAN.

Conclusion :

En somme, les données de nos patients corroborent celles de la forme classique de PKAN. La perspective de cette entité est le développement de thérapies rationnelles ciblant l'anomalie biochimique primaire, avec des composés qui contournent l'enzyme PANK2 défectueuse, notamment la fantaséine, la phosphopanthéthéine et la coenzyme A.

BACKGROUND

NBIA comprises a heterogeneous group of rare and hereditary disorders characterized by iron deposition particularly in the basal ganglia and sometimes in the substantia nigra and adjacent areas (2). The NBIA shares common clinical features including motor disorders, particularly parkinsonism and dystonia, cognitive dysfunction, pyramidal signs, and retinal abnormalities (2,4). PKAN, formerly called Hallervorden-Spatz disease, due to mutations in the PANK2 gene is the most common NBIA (30-50% of NBIA cases) (2,5,7). It has 2 main presentations: The classic form usually starts in the first decade of life with severe dystonia, dysarthria, parkinsonism, pyramidal and visual signs, and less cognitive disturbances with an aggressive course, leading to death by the second decade of life (7). In the atypical form, neuropsychiatric disorders are common with a slower progression and a more benign course (2, 5). A brain magnetic resonance imaging (MRI) usually shows the eye of the tiger sign (5). Here, we describe four cases whose age of onset and clinical presentation suggests a typical form of PKAN.

CASE SERIES

Case 1

This 17-year-old woman from a consanguineous marriage came to our attention with a 5-year history of movement disorders and behavioral disturbances such as irritability. In her milestones, she was noticed to be clumsy and prone to fall. On neurologic examination, she had moderate dystonia in limbs and trunk but severe oromandibular dystonia with geste antagoniste (touching lips with index to be able to temporarily open her mouth). She had also a blepharospasm forming a Meige's syndrome. In addition, there was mild parkinsonism with tremor, akinesia and abnormal ocular saccades with retinitis pigmentosa. Brain MRI showed the typical eye of the tiger sign (Fig. 1A). She was treated by trihexiphenidyl and botulinum toxin injections in the masseter and temporal muscles with respective improvement of the generalized and oromandibular dystonia.

Case 2

A 24-year-old woman from a consanguineous marriage presented early in her life some gait disorders with postural instability. By the age of 19, she also started having movement disorders with neurobehavioral difficulties (e.g. depression and impulsivity). Her sister had a similar problem. On neurologic examination, there was limbs dystonia and severe oromandibular dystonia causing speech and swallowing difficulties. This was often complicated by the temporomandibular joint luxation. She also had a parkinsonism. Symptoms were very slowly progressive with sometimes dystonic crisis. Brain MRI disclosed the typical eye of the tiger sign (Fig. 1B). As a treatment she received trihexiphenidyl and botulinum toxin injections in medial pterygoids and subhyoid muscles with a favorable outcome.

Case 3

This 19-year-old man from a consanguineous marriage consulted for movement disorders and behavioral difficulties evolving for 5 years. From the age of 7, he had gait disorder with prone to fall. On examination he had generalized dystonia affecting the 4 limbs predominantly upper limbs (left > right) with fixed spastic dystonia; cervical dystonia and oromandibular dystonia with speech and swallowing disorder. He also had

akinesia, pyramidal signs and retinitis pigmentosa. Blood cooper level was normal. A brain MRI revealed the typical eye of the tiger sign (Fig. 1C). He was treated by Baclofen and trihexiphenidyl with a slight improvement.

Case 4

This 9-year-old girl from a consanguineous marriage came to our attention with a 2-year history of progressive four limbs dystonia. In her milestones, gait was delayed with clumsiness and falls. The neurological examination found generalized dystonia affecting limbs, with laterocollis and oromandibular dystonia with speech difficulties. In addition, she had pyramidal signs, athetosis and behavioral impairment (e.g. hyperfamiliarity). Her brain MRI showed the typical eye of the tiger sign (Fig. 1D). The child's DNA screening found a c.303_304del: p.S101fs mutation in the PANK2 gene. She was treated by trihexiphenidyl with partial improvement.

DISCUSSION

We reported 4 cases of classic PKAN retained on clinical data and MRI. Other conditions that may exceptionally give the « eye of the tiger sign » would exhibit different clinical phenotypes and thus were not discussed in our cases. The mean age of onset was 5.75 years (probably before due to lack of accurate data) ; in the literature it is 3.4 years old (5). There is a parental consanguinity in all cases suggesting an autosomal recessive pattern. Indeed, PKAN is an autosomal recessive disorder characterized by mutations in the gene encoding a mitochondrial pantothenate kinase (PANK2) at locus 20p13-p12.38 [8]. Most PANK2 mutations are missense variants; especially the c.1561G>A missense mutation is the most common cause of PKAN (5). Our case 4 was the only one to benefit from genetic research finding the c.303_304del: p.S101fs mutation in PANK2 gene.

Clinical presentation of our patients was superimposed on that described in literature; Oromandibular dystonia was constant and was often complicated by dysarthria and dysphagia. It became generalized afterwards. Indeed, in classic PKAN, the majority of patients have oro-bucco-lingual dystonia and dysarthria; dystonia is therefore the main symptom; it can be generalized (8). Moreover, we had a parkinsonism in 2 patients, athetosis and pyramidal syndrome. These phenotypes are rarely described (5). Retinitis pigmentosa may occur in two-thirds of patients, associated or not with acanthocytes in blood cells (5,8). Two of our patients had retinitis pigmentosa (case1 and case3). Our 4 patients had moderate neuropsychiatric disorders with predominant behavioral disorders; in classic PKAN, one-third of patients have neuropsychiatric manifestations including behavioral difficulties (5).

Some affected children often have a history of nonspecific features prior to presentation, including clumsiness, dyspraxia, and motor/global neurodevelopmental delay (5). All our patients presented these symptoms several years before the onset of disease.

The progression of PKAN is characterized by cognitive and motor decline; the majority of individuals (85%) become wheelchair bound within10-15 years of diagnosis in the classic PKAN (8). Death is usually secondary to respiratory infections, cardiorespiratory complications, malnutrition state and, rarely, status dystonicus (8). Our patients are currently stabilized under treatment but the follow-up period is insufficient to confirm a favorable outcome. It is likely that deterioration would occur, leading to discuss other therapeutic methods especially deep brain stimulation.

The imaging was typical in our 4 patients showing the "eye-of-the-tiger" sign indeed this aspect is the characteristic feature on neuroimaging of PKAN (5). It is defined as a central region of signal hyperintensity reflecting gliosis and edema, and a surrounding hypointensity caused by iron accumulation in the globus pallidus (6). Although pathognomonic of PKAN, this specific MRI sign may be absent in authentic PKAN cases especially in the early or late disease stages (2,6). Otherwise, this sign has been reported to occur as an imaging phenocopy in other conditions, such as neuroferritinopathy, Wilson's disease, mitochondrial membrane protein-associated neurodegeneration, multiple system atrophy, and in healthy adults (5,6) ; but in those cases, careful assessment often reveals irregular contour and/or lateral displacement of the central hyperintensity (4). Hyposignal can also be observed in substantia nigra indicative of iron deposition.

There is no current specific therapy to stop disease progression; PKAN patients require multidisciplinary care. In their study, Cossu et al gave deferiprone to 6 patients with a 4 years follow-up; 5 patients were

stabilized suggesting efficacy and safety of deferiprone especially in adult patients at early stage of the disease (1). In selected cases of PKAN with drug-resistant dystonia, GPi DBS has been considered with results ranging from excellent to very modest improvement (3).

In PKAN patients who have residual PANK2 activity, the possibility of using high-dose pantothenate therapy has been considered (atypical forms) (5). Other symptomatic treatments are trihexiphenidyl, botulinum toxin, baclofen…(5). Our patients have all been treated with Trihexyphenidyl 5mg; Baclofen was given in one patient; 2 patients received botulinum toxin injections for oro-mandibular dystonia in a timely manner with a clear improvement.

CONCLUSION

In sum, the data of our patients corroborated those of the classic form of PKAN. Although the genetic assessment could only be performed in one case; the diagnosis in the other patients was based on the "eye-of-the-tiger" sign in an evocative clinical context thus excluding the differential diagnoses mentioned above. The perspective in this entity is the development of rational therapeutics targeting the primary biochemical anomaly, with compounds that bypass the defective PANK2 enzyme including phantasein, phosphopanthethein and coenzyme A.

Abbreviations

NBIA: Neurodegeneration with brain iron accumulation

PKAN: Pantothenate kinase-associated neurodegeneration

MRI: magnetic resonance imaging

MPAN: mitochondrial membrane protein-associated neurodegeneration

Author roles:

All authors read and approved the final manuscript.

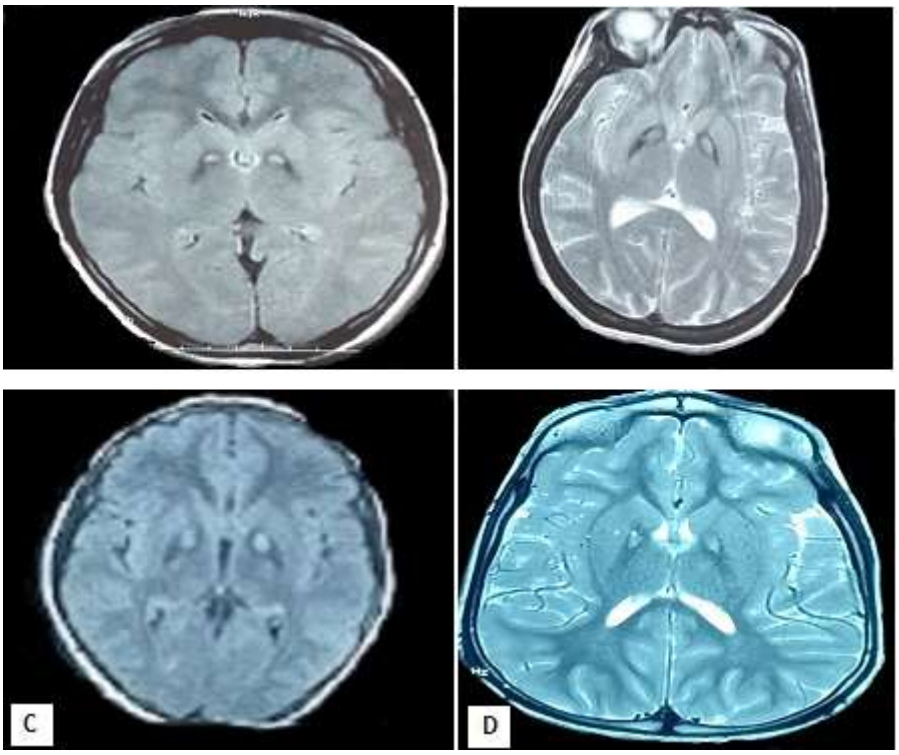

Figure 1: A, B, C and D: axial brain magnetic resonance images with typical eye of the tiger sign in Patients 1, 2, 3 and 4 respectively.

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