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Case report

First report of co-morbidity of pantothenate kinase-associated neurodegeneration and three types of chronic hemolytic anemias

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HIGHLIGHTS

- This is the first report of comorbidity of PKAN, β-thalassemia-major, sickle cell disease and G6PD deficiency.
- We highlight the pathophysiology of comorbidity of PKAN and chronic hemolytic anemias.
- A missense mutation in homozygous status in PANK2 gene on chromosome 20p13.

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ABSTRACT

Background: Pantothenate kinase-associated neurodegeneration (PKAN), sickle cell anemia, and thalassemia are autosomal recessive disorders that can cause iron deposition in tissues during childhood. PKAN is characterized by accumulation of iron in the basal ganglia causing progressive extrapyramidal manifestations. Thalassemia and sickle cell disease can cause iron overload and deposition in tissues, including central nervous system.

Presentation of case: we herein report the first report of comorbidity of PKAN, β-thalassemia-major, sickle cell and glucose-6-phosphate dehydrogenase deficiency (G6PD) anemias in a 9 years old Saudi female patient who presented with gait disturbance, speech difficulty, and progressive movement disorders of the neck, upper and lower limbs.

Conclusion: Although extremely rare, β-thalassemia-major, sickle cell and G6PD anemias can be associated with PKAN. It is unknown whether this association is random or due to an unknown factor that may have caused several mutations.

1. Introduction

Neurodegeneration with brain iron accumulation (NBIA) comprises a heterogeneous group of progressive complex motor disorders characterized by the presence of high iron deposits in the brain parenchyma, particularly within the basal ganglia [1]. One of these disorders is pantothenate kinase-associated neurodegeneration (PKAN) which is an autosomal recessive neuroaxonal degeneration [2]. The defect in pantothenate kinase-2 (*PANK2*) gene is predicted to cause the accumulation of cysteine. Cysteine binds to iron and accumulates in the globuspallidus, causing oxidative stress [3]. Clinical manifestations involve nearly all body systems, including the central nervous system in the form of stroke, febrile seizures, headache, paraplegia, epileptic seizures and localized sensory neuropathy [5].

Sickle cell anemia and thalassemia major are both hemoglobinopathies associated with iron overload [6].

2. Casereport

We report the case of a nine-year-old Saudi female patient who presented at the age of 6 years with gait disturbances and

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pronounced tendency to fall. Within few months, she developed rapidly progressive movement disorders in the neck, upper limbs, and lower limbs, losing completely the ability to walk. This was associated with speech and swallowing difficulty, constipation and repeated bronchoaspiration.

The patient was known to have sickle cell disease, β-thalaasemia-major and G6PD deficiency, confirmed by hemoglobin ectrophoresis and G6PD enzyme assay, and history of repeated blood transfusions. Her parents are second-degree relatives with family history of sickle cell disease and β-thalassemia-major.

On examination, the patient was disoriented to time, person and place. She was non-cooperative with poor cognitive functions. Weight and height evidenced severe failure to thrive. Hirsutism, and pallor were also present. There was noorganomegaly. Neurological examination showed microcephaly, increased both axial and limb tone, exaggerated reflexes, bilateral positive extensor plantar reflex, dystonia, athetosis and contracture deformities in both upper and lower limbs. Eye fundus examination was normal bilaterally.

Laboratory investigations showed microcytic hypochromic anemia (hemoglobin ranges 5.9–8gm/dl) with high RDW 30.3% (normal 11.5–16.5), reticulocytic count 21.15 (normal 0.4–1.5). Serum iron 5 μmol/L (normal 9–32), TIBC 26 μmol/L (normal 44.8–80.6), serum ferritin 903.7 ng/ml, LDH 1773 μ/L (normal 370–840), ceruloplasmin 0.348 g/L (normal 0.16–0.36) and copper content 112.6 μg/dL (normal 63.7–140.12 μg/dL). Her initial hemoglobin electrophoresis showed HbA is 0%, HbA2 is 3.5%, HbF is 7.5% and HbS is 89%. Red cell G6PD activity was deficient. Owing to the genetic heterogeneity of these disorders, genetic testing was not possible.

In a brain MRI, T2-weighted imaging showed the typical "eye of the tiger sign" on both brain hemispheres (Fig. 1). Abdominal MRI showed liver iron concentration 63 μmol/g. The initial EEG showed normal background tracing with frequent episodic epileptic discharges-bifrontal and central in the form of high voltage sharp waves. Motor neurography was normal.

Genetic testing for PKAN was done and revealed, 1561 G > A missense mutation in homozygous status in *PANK2* gene on chromosome 20p13.

Patient is currently on valproic acid, carbamazepine and topiramate for seizures, baclofen oral and intra thecally for spasticity and L-dopa for the extrapyramidal movements. There is no significant improvement in the spasticity, dystonia and athetotic movements.

3. Discussion

Iron is vital for normal neuronal metabolism; however excessive iron may beharmful [7]. There are many types of neurodegenerative

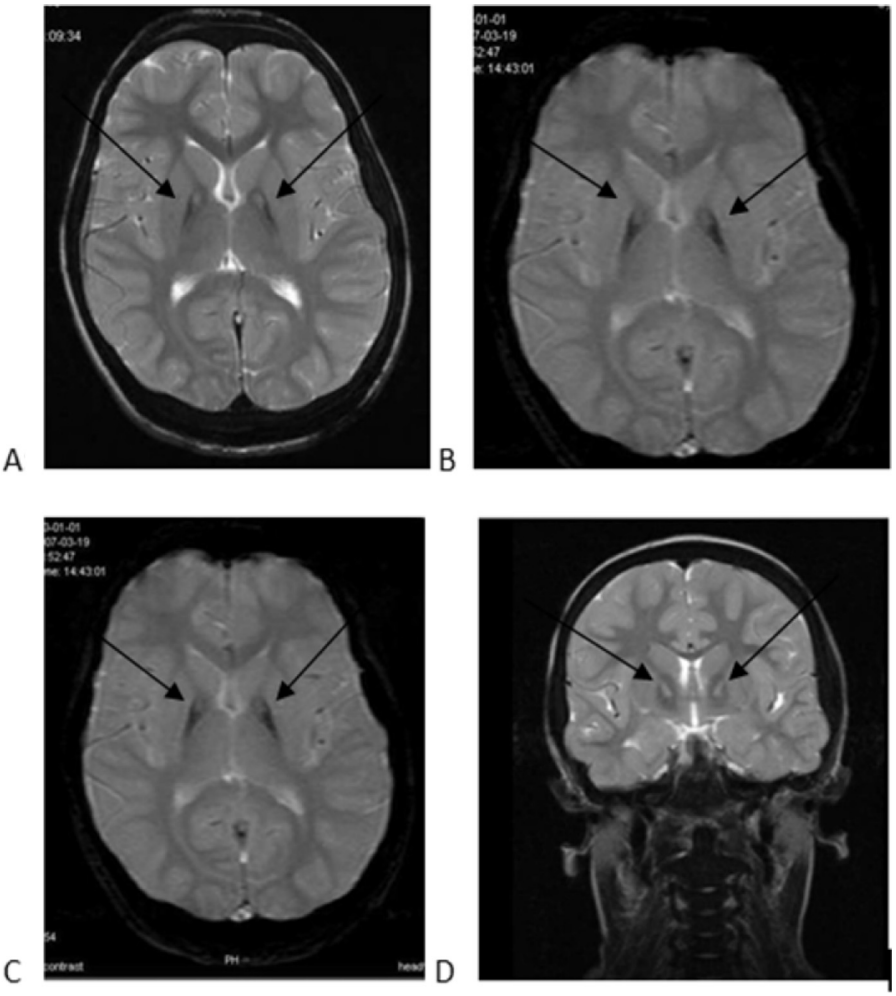

Fig. 1. brain MRI, T2-weighted imaging showed the typical "eye of the tiger sign" on both brain hemispheres.

disorders with brain iron accumulation (NBIA) types that can present during childhood. One of them is the PKAN, caused by mutation in *PANK2* gene, PKAN has 2 main forms: (1) the classical early onset form, and (2) the late onset form [8]. PKAN has a worldwide prevalence of 1–3 per a million [2]. PKAN has been previously reported in Saudi Arabia by Alotaibi and his group [9].

Our patient had all manifestations of the classic PKAN; extrapyramidal features clumsy with gait problems secondary to dystonia, corticospinal tracts signs as hypertonicity, hyperreflexia, spasticity, and upgoing plantar responses and dysphagia with feeding difficulties and gastroesophageal reflux that contributed to malnutrition and aspiration pneumonia. These patients are likely to be misdiagnosed early in the course of illness, because of the slow progression before the onset of dystonia and unless there is positive family history, the diagnosis is usually late.

An “eye of the tiger sign” is a specific MRI finding, characterized by low-signal intensity rings surrounding the central high signal intensity regions in the medial aspect of bilateral *globuspallidus* on T2-weighted scan. The surrounding hypointensity of the *globuspallidus* is due to the accumulation of excess iron. The central hyperintensity is possibly due to gliosis. This is a key diagnostic feature of PKAN, which was typically present in our patient. Zhou et al. [8] demonstrated that PKAN is caused by mutation in PANK2 gene, located on short arm of chromosome 20 (20p13) [10], which was the mutation reported in our patient.

There are marked regional variations in the prevalence of sickle cell disease and β-thalassemia in Saudi Arabia, with the eastern region having the highest prevalence [11] This is the region from where our patient originated. Strange enough was the coexistence of 3 hemolytic diseases in our case; B-thalassemia-major, sickle cell anemia and G6PD deficiency.

The co-existence of sickle cell anemia in our patient may be a contributing factor to the existing neuropsychological manifestations through overt or silent cerebral infarcts. The co-existence of β-thalassemia may have also contributed to the iron accumulation in the CNS secondary to repeated blood transfusions.

The rapid progression of neurological symptoms in our patient could be attributed to that the increased oxidative stress caused by PANK2 enzyme deficiency enhanced by iron overload secondary to the repeated blood transfusions needed for the β-thalassemia.

After an exhaustive search of the literature, we did not find any other cases of patients with comorbidity of sickle cell anemia, β-thalassemia, G6PD deficiency and PKAN, nor of any common super ordinate syndrome. The genes of these diseases are located on different chromosomes loci; the PANK2 gene is on chromosome 20 [11], that of sickle cell anemia on chromosome 11 [12], that of thalassemia on chromosome16 [12], and that of G6PD deficiency on the X chromosome [13]; however an unknown factor may have caused several mutations with the clinical consequence of several different diseases.

In our opinion, the unfortunate coincidence of these four different recessive inherited diseases in our patient was attributed to the high degree of consanguinity accumulated over more than 5 generations. PANK has worldwide prevalence is 2–3 per million [2]. In eastern region of KSA, Sickle cell B-thalassemia has a prevalence of around 10% [14]. G6PD has a prevalence of 6% in KSA [15]. Hence if we use a mathematical model, the likelihood of all occurring in one individual is 12–18 per 1 billion which is in favor of being a chance occurrence.

4. Conclusion

Although extremely rare, β-thalassemia-major, sickle cell and G6PD anemias can be associated with PKAN. It is unknown whether this association is random or due to an unknown factor that may have caused several mutations.

Ethical approval

Reporting this case report was approved by the local research and ethical committee.

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Authors' contributions

IT: drafted the manuscript and followed up the patient.

NK and EA: drafted the manuscript, reviewed literature.

EE, MA, HA, MS: followed up the patient, ordered diagnostic investigations and designed treatment plan.

All authors revised the manuscript and approved it for submission.

Conflicts of interest

The authors have no potential conflicts of interest.

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