

Case report

Cases of neuro-ferritinopathy from Sudan

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Abstract:

Neuro-ferritinopathy (NBIA) is a bag of diseases due to abnormal iron metabolism. It has different underlying genetic and enzymatic abnormalities. On the other hand, they share some radiological features. Patients present with a wide range of cerebral symptoms and signs. Diagnosis depends on the semiology, genetic testing and MRI imaging. No specific treatment is available for these cases and they represent a challenge to the treating neurologist. Here we illustrate two interesting cases with their clinical and imaging findings to raise the awareness of such rare diseases and help diagnosing them in a low- resource setting.

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Introduction:

Neuro-ferritinopathy is a group of diseases due to abnormal metabolism of iron. It contains around 10 mutations that include a ceruloplasminemia (*Cp*), ferritin light chain (*FTL*, *FA2H*), phospholipase-A2 (*PLA 2G6*), Co enzyme A synthetase (*COASY*). Other types may be due to abnormalities in the enzymes of pantothenate-kinase 2 (*PANK2*) which is an autosomal recessive disorder that has a severe childhood and an adult form⁽¹⁾. In *PANK2*, the cognition is usually spared and the golbus pallidus shows bilateral symmetrical involvement referred to as eye of the tiger sign on imaging⁽²⁾.

In fatty acid 2 hydroxylase (*FA2H*), the age of onset is after 4 years. The clinical manifestations included spasticity, dystonia and later cognitive and cerebellar dysfunction⁽³⁾.

In phospholipase-A2 (*PLA 2G6*) related mutations⁽⁴⁾, the disease has a wide range of clinical features that include infantile, juvenile and late-onset neurodegenerative signs.

Excess iron may be detected in post-mortem studies of brains that have suffered Alzheimer's disease or Parkinson's disease possibly due to oxidative

stress effect of iron. The iron regulation may be genetically disturbed; also in Frederick's ataxia⁽⁵⁾.

Some neuro-ferritinopathy disorders are inherited in an autosomal dominant manner with 100% penetrance. Children will have 50% chance of inheriting the disease. In families with known genetic pathology, prenatal diagnosis is possible⁽⁵⁾. The common presentation of this disease is by abnormal movement disorder in the form of chorea or dystonia. This may affect limbs or trunk depending on the duration of the illness. Later in the disease, patients may manifest cognitive or behavioural changes. There is a characteristic action-specific dystonia with peculiar speech dysarthrophonia. Other signs include frontalis over-activity and oro-facial dystonia. Some therapies may result in partial response in this condition like L-dopa, tetrabenazine, orphenadrine, benzhexol, sulpiride, diazepam, clonazepam, deanol and botulinum toxin⁽⁶⁾. Moreover, good nutrition and physiotherapy will help delay of complications.

Neuro-ferritinopathy is suspected in patients with adult-onset movement disorders, positive family history and, in advanced cases, the cystic changes in relevant areas of the brain on MRI scans. The

cavitation in the external globus pallidus and head of the caudate correlates with the severity of the Unified Dystonia Rating Scale (UDRS) ⁽⁷⁾ .

Hence, the diagnosis in neuro-ferritinopathy may be made by the typical clinical and radiological features. The latter may reflect cystic changes in the globus pallidus and putamen. The confirmation of diagnosis is by single, multiple genes testing or whole genomic testing ⁽⁶⁾. Other known mutations in neuro-ferritinopathy group included *COASY C19 or f12, WDR45 and DCAF17 (C2orf37)* ⁽⁸⁾ .

Table 1. Forms of neuro-ferritinopathy (NBIA) ascribed to and the respective gene mutations.

NBIA subtype	Gene mutation
PKAN	PANK2
PLAN	PLA2G6
Neuro-ferritinopathy	FTL1
Aceruloplasminemia	Ceruloplasmin
BPAN	WDR45
Kufor-Rakeb syndrome	ATP13A2 (PARK9)
MPAN	C19orf12
FAHN	FA2H
CoPAN	CoASY
Woodhouse- Sakati syndrome	C2orf37

The MRI scanning has a significant input in the diagnosis of inherited conditions along with the semiology and the preferential signal changes noted in symmetry in the brain ⁽⁹⁾ .

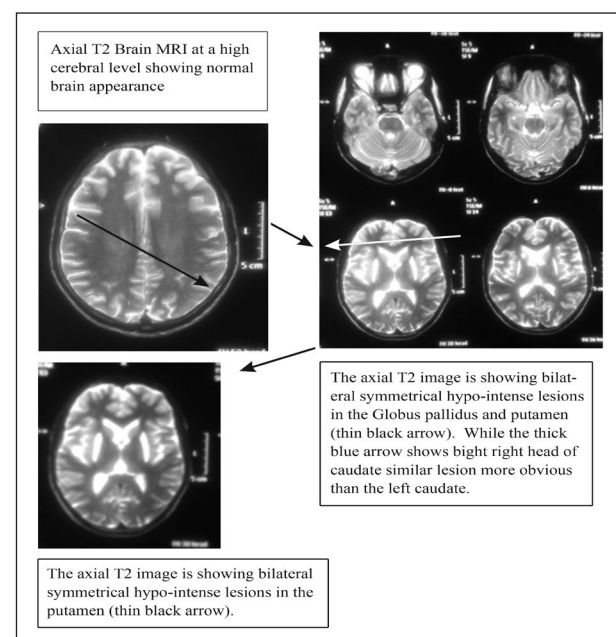
Cases Report:

Case one:

This is a case of a 22-year-old male from Khartoum. His clinical condition started 6 years before presentation with unexplained swallowing difficulties followed by speech difficulty. Within a year his gait started to be affected and he developed abnormal posture of both hands. He had to stop his

university studies in the first year. The patient did not manifest symptoms of cognitive dysfunction or urinary incontinence though his voice became dystonic. His past medical history is insignificant but his elder sister has similar milder condition. His clinical examination showed generalized dystonia with no cerebellar, pyramidal, neuropathic or cognitive dysfunction. However, he has some emotional liability. The systemic examination showed no skin rash, lymphadenopathy or thyroid enlargement. There was no evidence of small liver span, peripheral neuropathy, retinal changes or cardiac abnormalities. The routine blood tests including CBC/ PBP, TFT, LFT, U&Es and K F rings testing were all normal. He had normal copper and vitamins studies. PTH, Ca, Iron, TIBC and Ferritin were all normal.

MRI brain showed symmetrical deposition in the basal ganglia, mainly globus pallidus and putamen hypo-intensities and on the head of the right caudate nucleus mainly as shown below:



A trial of symptomatic treatment using Trihexyphenidyl tabs 10 mg increased to 15 mg over one month and treated for 3 months, reported no improvement in the patient dystonia. However, he developed intolerable side effects in the form of dry mouth, tremors and dose-related fever. The drug was stopped and his symptoms were relieved. The patient and family were counseled and he was advised to go for Deep Brain Stimulation (DBS) and genetic testing abroad.

The diagnosis on this case was based on the clinical features, family history and imaging. Due to underdeveloped local resources the globus pallidus and putamen hypo-intensities were used to augment the diagnosis. This finding may be used to diagnose such rare condition ⁽⁹⁾.

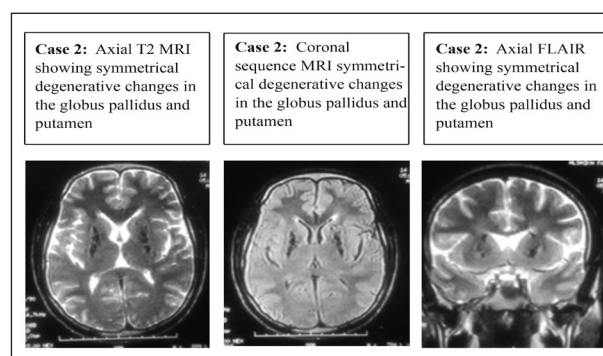
In view of the diagnosis and the intact cognitive functions, DBS will help the physical disability in this young adult and it was recommended as a treatment to purchase outside the country.

Case two:

This is a case of a 26-year-old male from Central Sudan. This patient problem started in 2016 with difficulty in walking and abnormal posture of the hands and legs. There were no symptoms of cerebral dysfunction or urinary incontinence. The clinical condition progressed slowly. His past medical history was insignificant. The clinical examination showed generalized dystonia with no cerebellar, pyramidal or cognitive dysfunction. However, he has some emotional liability. The systemic examination showed no skin rash, peripheral neuropathy, retinal changes, lymphadenopathy or thyroid enlargement. There was no evidence of small liver span or cardiac abnormalities. All the blood tests performed for case one were also normal in case two.

He was started on treatment for 4 months using L-Dopa / Carbidopa tablets 250/25mg half tab BD + Trihexyphenidyl 5 mg b.d. The patient reported mild improvement in the axial dystonia but he still suffers focal dystonia. Further plan for this patient

was similar to case one and abroad treatment with DBS was recommended. (MRI brain is shown below).



Discussion:

The two cases differ from the oldest case reported of familial Hallevorden Spatz disease previously described in a 68-year-old patient in that our patients are younger in age. However, it was similar to our cases as his symptoms included dystonia and eye lid dystonia which is evident in the two cases presented here. Moreover, the oldest case reported (age wise) presented with dementia, apraxia and incontinence. His autopsy showed brain atrophy with evidence of iron accumulation in the globus pallidus, caudate and substantia nigra. There are radiological similarities also as the radiological features in our cases were evident in the globus pallidus; putamen and head of the caudate (*see case one images*).

In a study which enrolled 49 cases of neuro-ferritinopathy cases, 59% of cases had genetic mutation in PANK2 gene. The radiological appearance of the eye of the tiger sign was demonstrated reflecting the central hyper-intensity surrounded by peripheral hypo-intensity in the globus pallidus in T2 images. It is important to mention that before the hyper-intensity develops, the mutation-related cases will show only globus pallidus hypo-intensity at least for the first 3 years. In the two cases presented here, this characteristic sign was not shown on their scans. Hence, not confirmatory, but this may not favor the presence of PANK2 mutation in them⁽²⁾.

There are obvious differences between our cases and the reported cases of fatty acid 2 hydroxylase

(FA2H). This includes the age of onset of dystonia in childhood versus adulthood onset in our cases. Moreover, the associated cerebellar and spastic paraparesis signs which are not present in these two cases reported here. The radiological MRI findings in (FA2H) included cerebellar atrophy and thin corpus callosum which were not demonstrated in the reported cases here and may help to some extent to exclude this mutation ⁽³⁾.

Though, the reported cases of PLAN (phospholipase associated neuro-degeneration) may show globus pallidus hypo-intensities as seen in our reported cases but the patients are usually mentally subnormal and their disease starts in childhood. Just to mention for the purpose of discussion that our patients were mentally normal and one of them was a university student ⁽⁴⁾.

These cases represent a challenging type of diagnosis that is poorly understood, lacks specific tests (at least in our setting) as well as not having a known treatment. However, revealing the diagnosis will help explaining the type of movement disorder that happens in these patients and will keep the clinical awareness standing for such a rare diagnosis. Grouping such cases may reveal a special clinical phenotype that may direct genetic testing in such an under-resourced country. The clinical phenotype plus the developing MRI techniques may generate a scoring system that enables more near final diagnosis in the poor availability of genetic and rare enzymatic testing in under-developed countries.

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