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Rare neurogenetic diseases with paramagnetic material accumulation in the brain: A case series study

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Abstract

Aim: To draw attention to rare neurogenetic diseases that are characterized by paramagnetic substance accumulation in the brain by sharing 12 subjects who presented with different clinical manifestations.

Material and methods: Twelve patients who presented to our clinic between 2009 and 2019 with different complaints and were diagnosed as having FAHR syndrome, PKAN and Wilson disease were analyzed retrospectively. Presentation symptoms, physical examination findings, radiological and laboratory findings and treatment responses of the patients were evaluated.

Results: Seven of the 12 subjects admitted to our clinic over a 5-year period were female, and 5 were male. The median age at the time of presentation was found to be 31-34 years (21-67). All of the patients received a new diagnosis after presentation. The patients presented with various complaints such as progressive walking difficulties, imbalance, disorder of writing ability, tinnitus, agitation, constant crying, convulsion, frequent falls, speech disorder, and slow movement. In the etiology, 4 of the patients were diagnosed with PKAN, 6 patients were diagnosed with FAHR syndrome and 2 patients were diagnosed with isolated neurological symptoms.

Conclusion: Most of the recent developments related to the roles of metals in neurological diseases have arisen from the identification of new genetic diseases. These rare neurogenetic diseases, which can be manifested with many different clinical features ranging from pyramidal and extrapyramidal findings to neuropsychiatric findings, should be considered in the differential diagnosis since they often affect the young population and the rates of disability and mortality can be reduced with early diagnosis.

Key words: Wilson disease, Fahr disease, accumulation of paramagnetic materials in the basal ganglia, pantothenic kinase-associated neurodegeneration

Introduction

Diseases that are characterized by accumulation of paramagnetic materials in the brain are extremely rare and difficult to identify. Fahr syndrome, Pantothenic Kinase Associated Neurodegeneration (PKAN) and Wilson disease (WH) are defined as neurodegenerative diseases with a variable and wide neuropsychiatric spectrum, which are associated with accumulation of paramagnetic materials in the brain.

Fahr syndrome is a rare disease characterized by calcification in the basal ganglia, dentate nucleus of the cerebellum, and centrum semioval, usually with an autosomal dominant inheritance, but sporadic cases and autosomal recessive inheritance have also been observed [1]. The syndrome was described for the first time by Fahr in 1930. Neuropsychiatric, extrapyramidal and cerebellar symptoms, speech disorder and dementia are frequently detected. However, there are also subjects who remain asymptomatic despite extensive calcium accumulation [2].

PKAN, formerly known as Hallervorden-Spatz syndrome, is a rare hereditary neurological movement disorder characterized by progressive degeneration (neurodegenerative disorder) of specific areas in the central nervous system (CNS) [3,4].

The course in PKAN is associated with accumulation of iron in the brain. It is a type of neurodegeneration that is characterized by progressive abnormal involuntary movements, changes in muscle tone and postural disorders (extrapyramidal) [4,5].

Wilson disease (WH) is genetic disorder of the copper metabolism characterized by cirrhosis and degenerative CNS disorder. Clinical presentation can be quite variable. All forms of acute and chronic liver disease can cause mild to severe neurological diseases, psychiatric problems, bone deformities, hemolytic anemia, and endocrine findings [6]. In this article, we would like to draw attention to rare neurogenetic diseases that are characterized by paramagnetic substance accumulation in the brain by sharing 12 subjects who presented with different clinical manifestations.

Material and methods

The research was carried out in Bolu Abant İzzet Baysal Education Research Hospital. Necessary permissions were obtained to use hospital data for this study (approved by the letter dated 18/09/2019 with number 33443051-929-E.1647). Informed consent was taken from the patients who participated in the study. 12 subjects who presented with different complaints between 2014 and 2019 and were diagnosed as having FAHR syndrome, PKAN and Wilson disease, were analyzed retrospectively. Individuals who were detected to have accumulation of paramagnetic materials in the brain during the study period, were included in the study. The patients' symptoms and examination findings were recorded. Each patient's laboratory tests were evaluated. The patients' computed tomography (CT) and magnetic resonance imaging (MRI) findings were evaluated in terms of presence of paramagnetic material and presence of calcification, and the patients who were found to have accumulation of paramagnetic material, were included in the study. In addition, the patients' treatment and follow-up interviews and clinical features were recorded.

Patients who underwent tomography for causes such as a traffic accident and were incidentally diagnosed as having FAHR syndrome, and those with Wilson's disease who had normal imaging findings were excluded from the study.

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data are given as median (minimum - maximum) for continuous variables according to normality of distribution and frequency (percentage) for categorical variables. Continuous variables were analyzed with the Kruskal Wallis test. Categorical variables evaluated using the Chi-square tests. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

Seven of the 12 subjects admitted to our clinic over a 5-year period were female, and 5 were male. The median age at the time of presentation was found to be 32.5 years (range = 21-67). All of the patients received a new diagnosis after presentation. The patients presented with various complaints such as progressive walking difficulties, imbalance, disorder of writing ability, tinnitus, agitation, constant crying, convulsion, frequent falls, speech disorder, and slow movement. In the etiology, 4 (33.3%) of the patients were diagnosed with PKAN, 6 (50.0%) patients were diagnosed with FAHR syndrome and 2 (16.7%) patients were diagnosed with isolated neurological symptoms. In the subject number 8 who had FAHR syndrome, hypoparathyroidism was detected in laboratory tests. 25.0% of the PKAN cases, 50.0% of the FAHR syndrome cases, and 50.0% of the isolated neurological symptom cases were male. The median age at the time of presentation was found to be 31.5 years (range = 21-67) in PKAN cases, 38.5 years (range = 22-66) in FAHR syndrome cases, 28.6 years (26-31) in isolated neurological symptom cases. There was no significant difference between the patient groups in terms of gender and age (p=0.710, p=0.835, respectively). The subjects number 9 and number 10 were a mother-daughter pair and they had familial FAHR disease. The Subjects' demographic data, clinical and imaging findings and treatment schedule are summarized in Table 1.

Figure 1 - Case 9: 22-year-old female patient with FAHR disease, loss of signal secondary to accumulation of paramagnetic substance in the lentiform nuclei and thalamus on gradient echo on brain MRI in A shown with bold white arrows, hyperintense signal change on axial T1 sections in B shown with light white arrows, presence of calcification at the same levels on axial CT sections in C shown with fine white arrows.

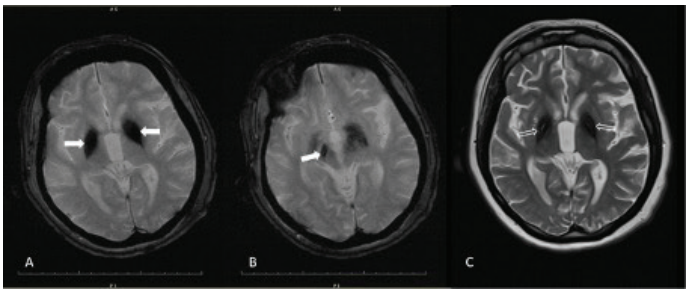


Figure 2 - Case 10: A 52-year-old patient with FAHR disease, calcifications marked with bold white arrows in the dentate nucleus in both cerebellar hemispheres in A, in the lentiform nuclei in the upper part and in the thalamus in the lower part in B, in bilateral periventricular deep white matter in C.

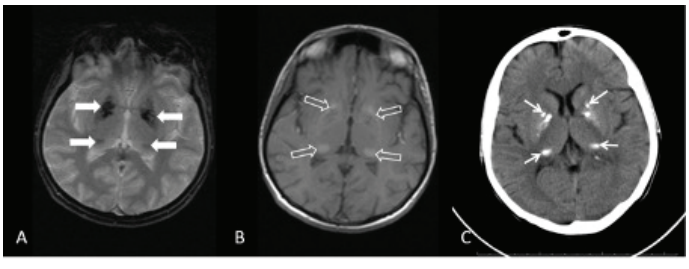


Figure 3 - Case 12: A 26-year-old patient diagnosed with Wilson disease, hyperintense signal changes secondary to the accumulation of substance in the right cerebellar hemisphere (A), brain stem (B), in both thalamus and basal ganglia (D) in axial T2 sections shown with white arrows. In C, face of the giant panda sign is being observed in the midbrain.

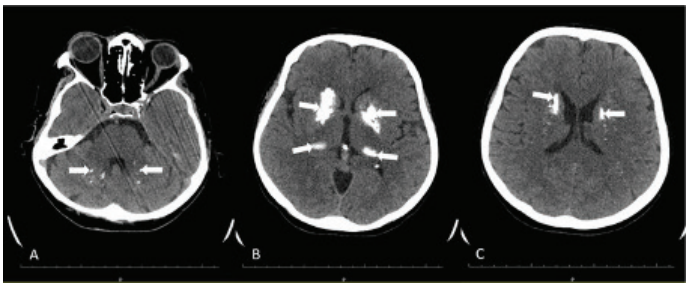


Table 1 The subjects' demographic data, clinical and imaging findings and treatment schedules

No, Diagnosis	Gender	Age	Clinical picture	Imaging finding	Treatment
1. PKAN	F	37	Progressive walking difficulty, diffuse spastic tetraparesis, extrapyramidal symptoms, forgetfulness, confinement to bed, epileptic seizure	Gradient echo showing accumulation of paramagnetic material in the globus pallidus and substantia nigra, hypointensity in T2 signal and Tiger's eye finding on MRI (Iron accumulation) (Figure 1)	Baclofen Chelation (Desferrioxamine)
2. PKAN	M	67	Progressive Cognitive impairment, need for help in daily activities, diffuse extrapyramidal symptoms, Parkinsonism findings	Paramagnetic substance accumulation on gradient echo in the substantia nigra and globus pallidus on MRI (Iron accumulation)	Anti-Parkinson, Antidepressant
3. PKAN	F	21	Progressive Writing Difficulty, Gait Disorder, Decline in Academic Success, Spastic Tetraparesis, Imbalance	Decrease in T2 signal extending to substantia nigra in bilateral globus pallidus, Tiger's eye finding and accumulation of paramagnetic substance in gradient echo on MRI (Iron accumulation)	Chelation (Desferrioxamine) Baclofen
4. PKAN	F	26	Progressive gait disorder, spastic tetraparesis, Gait disturbance, fall attacks, imbalance, PKAN 2 gene (-), partial response to chelation therapy in the patient who was being followed up with a diagnosis of celiac disease for about 15 years.	T2A hypointensity in the globus pallidus and substantia nigra on MRI, accumulation of paramagnetic substance in gradient echo (Iron accumulation)	Baclofen Chelation (Desferrioxamine)
5. FAHR	M	66	Epileptic seizure,	Symmetrical calcifications in bilateral globus pallidus, thalamus, centrum semiovale and cerebellar dentate nuclei on CT	Antiepileptic
6. FAHR	M	23	Tinnitus (ringing in the ears)	Calcification in bilateral basal ganglia on CT	Symptomatic Treatment
7. FAHR	F	34	Epileptic seizure,	Loss of signal secondary to paramagnetic substance accumulation in bilateral globus pallidus on MRI	Antiepileptic treatment
8. FAHR	M	43	Forgetfulness, sensation of diffuse numbness	T2A hypointensity and accumulation of paramagnetic material (Calcium accumulation) in gradient echo in basal ganglia on MRI	Calcitriol Ca preparations Hypoparathyroidism
9. FAHR	F	22	Syncope, panic attack, neuropsychiatric complaints, diffuse numbness and tingling, heart rhythm disorder	Calcification in the thalamus and lentiform nucleus on CT, T1A hyperintense signal change on MRI and accumulation of paramagnetic substance in the gradient echo (Figure 2)	Symptomatic Treatment Beta Blocker
10. FAHR	F	52	Palpitations, neuropsychiatric findings, tingling and numbness in the hands and feet	Calcifications in the cerebellum, dentate nucleus, thalamus and basal ganglia, periventricular deep white matter on CT, T1Ahyperintense signal change on MRI and accumulation of paramagnetic substance in gradient echo (Figure 3)	Symptomatic Treatment
11. Wilson disease	M	31	Hepatic cirrhosis, Kayser Fleisher (+),	T1A hyperintense signal change in bilateral basal ganglia and signal increase in corticospinal tract	Metalcaptase
12. Wilson disease	F	26	Speech disorder, nasal speech, tremor in hands, balance disorder, impaired cognitive function, speech disorder, neuropsychiatric disorder. Kayser-Fleischer ring	T2 hyperintense signal change in bilateral caudate nuclei, putamen, globus pallidus, mesencephalon and right cerebellar hemisphere on MRI (Figure 4)	Penicillamine Ferro fumarate

Discussion

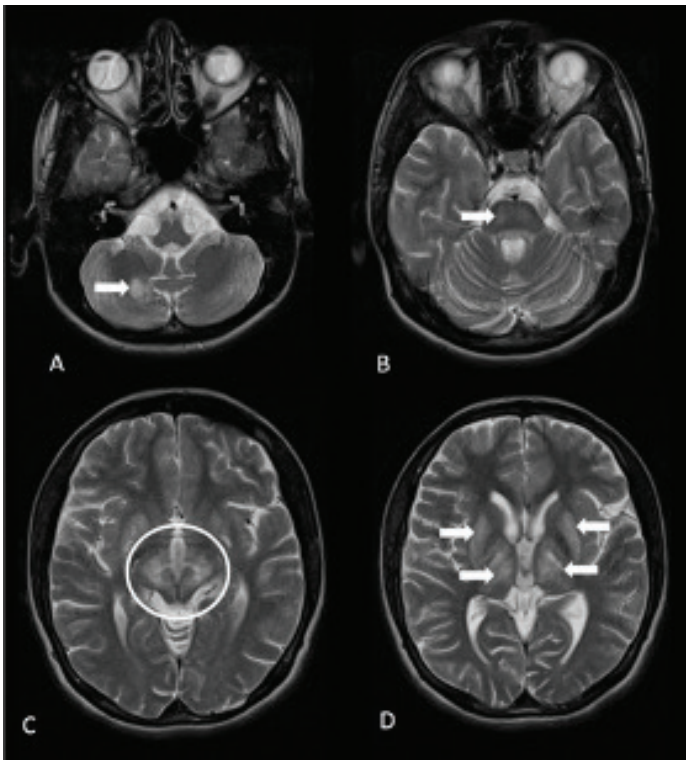
PKAN; Hallervorden-Spatz disease, known as pantothenate kinase-related neurodegeneration (PKAN), is a rare autosomal recessive neurodegenerative disease associated with iron deposition in the brain and characterized by progressive extrapyramidal dysfunction and dementia [7,8].

The exact etiology of PKAN is not fully understood. One of the hypotheses proposed is presence of insufficient cysteine dioxygenase leading to abnormal oxidation of lipofuscin to neuromelanin and abnormal iron accumulation in the brain. Although the globus pallidus and pars reticulata have a relatively higher iron content in healthy individuals, individuals with PKAN have an excessive amount of iron deposited in these nuclei [9,10].

Mutation in PANK2 (Gen band 20p13) explains mostly inherited cases of PKAN as the etiology of PKAN in various studies [11]. The prevalence of PKAN is 1-9 / 1000000. Classical presentation is between the ages of 7 and 15 years at the end of the first decade or in the first part of the second decade. PKAN is a disease characterized by corticospinal dysfunction and extrapyramidal findings such as dystonia, rigidity in muscles and choreoathetosis. In addition, mental changes and dementia, progressive disease and loss of patients in adulthood are other clinical features [12].

There is no effective medical treatment (Desferrioxamine, Coenzyme A and high dose pantothenate administration). Stereotactic surgical methods such as thalamotomy and pallidotomy are used for dystonia [8]. Our cases are compatible with these literature data; symptoms started in childhood and all

Figure 4 - Case 1: 37-year-old, Female patient, signal loss secondary to accumulation of paramagnetic substance in the globus pallidus and right substantia nigra on gradient echo in A and B, respectively in the patient was being followed with a diagnosis of PKAN. In C, axial T2 images show hypointense signal change in both globus pallidus and accompanying central longitudinal high signal line (eye of the tiger sign).



of our subjects had cognitive impairment with extrapyramidal findings [4]. Again, no clinical response was received, and clinical progression continued despite chelation (Desferrioxamine) treatment applied to our patients.

Patients with Fahr Syndrome; Fahr syndrome is a rare disease characterized by calcinosis developing as a result of disorder of the calcium and phosphorous metabolism in the cerebellum, thalamus and basal ganglia with a course associated with neurodegenerative disorders; accumulation of calcium and various minerals can be demonstrated by brain tomography (CT) [1,13].

Various causes including genetic, developmental, metabolic, infectious, sporadic and other factors as well as hypoparathyroidism or pseudohypoparathyroidism, have been reported. In addition, cases of familial Fahr syndrome have been reported; most of these cases have been shown to have autosomal dominant inheritance, and some cases with autosomal recessive inheritance have also been shown [14,15].

Clinically, Fahr syndrome usually starts with getting fatigued easily, unsteady gait, slow speech or speech impairment, difficulty in swallowing, involuntary movements or muscle cramps, and continues with neuropsychiatric symptoms such as psychosis, dementia and personality changes. Clinical findings are mostly seen in the 4th and 5th decades [16].

The most commonly used method in the diagnosis of Fahr syndrome is cranial computed tomography. With the use of CT, the frequency of calcifications in basal ganglia increased in cases with Fahr syndrome. Especially calcification located symmetrically in the dentate nucleus, basal ganglia, thalamus and centrum semiovale, is shown by CT [17,18].

Various agents with regulation of calcium metabolism have been tried in the treatment of Fahr syndrome, including nimodipine, a central nervous system-specific calcium channel blocker, but treatment has failed. In addition, etidronate disodium has been shown to resolve symptoms without being effective in reducing calcifications. Generally, patients are followed up with symptomatic treatment [19]. Our cases were compatible with these literature data and no significant difference was observed.

Wilson disease (WH) is an autosomal recessive disease that develops as a result of copper metabolism disorder. Many organs, especially the liver and brain, may be affected by copper accumulation in the affected people. Wilson's disease is fatal if untreated. The frequency of the disease varies between 1/5000 and 1/30000. It is associated with mutation in the the ATP7B gene located in the long arm of the thirteenth chromosome (13q14 – q21). It encodes the transmembrane protein ATPase (ATP7B). Disruption of ATP7B function expressed in the hepatocytes causes accumulation of copper in the liver, causing WH. The symptoms of the disease usually begin in the 2nd and 3rd decades [20,21].

Clinical manifestations of Wilson's disease [20]

- Hepatic
- Persistently elevated liver enzymes
- Chronic hepatitis
- Cirrhosis (decompensated or compensated)
- Fulminant hepatic damage (+/- hemolytic anemia)
- Neurological
- Dysarthria-Anarthria, Dysphagia, Dystonia, Chorea
- Tremor (often "flapping")
- Cognitive impairment, Gait disturbance
- Parkinsonism (rigidity, bradykinesia, postural changes)
- Pseudobulbar paralysis, Seizures, Sleep disorder
- Ophthalmic
- Kayser-Fleischer ring
- Sunflower cataract
- Psychiatric
- Depression
- Anxiety
- Personality changes
- Psychosis
- Other systems (rare)
- Renal failure, aminoaciduria and kidney stone
- Amenorrhea, ovarian dysfunction, infertility, abortion
- Cardiomyopathy, arrhythmias
- Anemia, thrombocytopenia

Serum aminotransferase activity is generally increased excluding very early stage disease. In a typical picture, serum ceruloplasmin level is low (less than 0.2 g/L, Normal: 0.2-0.5 g/L), and serum copper level is high. In almost all patients, copper excretion is increased in 24-hour urine, which is a more sensitive measurement compared to serum copper and ceruloplasmin levels [22,23].

The most reliable laboratory test in WD, is liver biopsy. Increased amount of copper in dry liver tissue greatly supports WD. Signal changes in Putamen, globus pallidus, caudate nucleus, thalamus, mesencephalon, pons and cerebellum on cranial MR, are the most striking findings [6,24].

The Kayser Fleischer ring detected in the eye as a result of deposition of copper circulating in serum on the Descemet's membrane on the inner surface of the cornea, is pathognomonic. The most commonly used chelating agents in Wilson disease are Penicillamine and Trientine. In our patients, the diagnosis was made with recognition of Kayser Fleischer ring while liver function tests (KCFT) were within the normal limits. In patients with clinical suspicion, the Kayser Fleischer ring should be

investigated in the eye when diagnosing Wilson Disease, even if LFTs are normal [20].

Conclusion

In this study, in which we presented diseases characterized by accumulation of paramagnetic materials in the brain, the data of our patients were consistent with the results in the literature.

In conclusion, it can take a long time to recognize these diseases. Paramagnetic material accumulation in the brain may be considered in the differential diagnosis in people with abnormal and not fully explained neurological findings.

Most of the recent developments related to the roles of metals in neurological diseases have arisen from the identification of new genetic diseases. In this retrospective study, the most important limitation was the fact that genetic studies were not performed, or the data of genetic studies could not be reached.

These rare neurogenetic diseases, which can be manifested with many different clinical features ranging from pyramidal and extrapyramidal findings to neuropsychiatric findings, should be considered in the differential diagnosis since they often affect the young population and the rates of disability and mortality can be reduced with early diagnosis.

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