Fahr's syndrome in Southern Tunisia: A broad spectrum of clinical and etiological features

Le syndrome de Fahr dans le Sud Tunisien : Description clinique et étiologique

Sahar El Aoud, Mouna Elleuch, Nadia Charfi, Faten Hadj Kacem, Mouna Mnif, Nabila Rekike, Fatma Mnif, Mohamed Abid.

Service d'Endocrinologie, CHU Hédi Chaker, sfax / Université de sfax,

RÉSUMÉ

Objectif: Nous décrivons le profil clinique et étiologique des patients atteints d'un syndrome de Fahr (SF).

Méthodes: Seize patients ayant un SF ont été rétrospectivement colligés entre 1999 et 2014.

Résultats: L'âge moyen au moment du diagnostic était de 44,68 ans (11-67 ans). Les principales manifestations neurologiques de présentation étaient les crises épileptiques dans 6 cas, les céphalées dans 5 cas et le syndrome parkinsonien dans 3 cas. Des troubles psychiatriques ont été observés chez 2 patients incluant la perte de mémoire et l'irritabilité. Des signes cliniques d'hypocalcémie ont été observés dans 7 cas. La valeur moyenne de l'hypocalcémie était de 1,69 mmol / l.

Les étiologies comprenaient l'hypoparathyroïdie idiopathique chez 4 patients, la pseudohypoparathyroïdie chez 5 patients, l'hypoparathyroïdie secondaire, l'hypovitaminose D isolée et la radiothérapie cérébrale dans un seul cas pour chacune et la maladie de Fahr chez 4 patients. La substitution orale du calcium et de la vitamine D a été instaurée chez des patients présentant des troubles de la parathyroïde avec une évolution favorable.

Conclusion: Dans cet article, nous proposons de discuter les manifestations cliniques du SF, ses étiologies, en particulier les troubles parathyroïdiens et ses modalités thérapeutiques.

Mots-clés

syndrome de Fahr, hypocalcémie, hypoparathyroïdie, pseudohypoparathyroïdie.

SUMMARY

Aim: We describe the clinical and etiological profile of patients with Fahr's syndrome (FS).

Methods: Charts of sixteen patients diagnosed with FS between 1999 and 2014 were retrospectively assessed.

Results: The mean age at diagnosis was 44.68 years (11-67 years). The most main presenting neurological features were seizures in 6 cases, headaches in 5 cases and parkinson's syndrome in 3 cases. Psychiatric disorders were observed in 2 patients including memory loss and iritability. Hypocalcemia clinical features were observed in 7 cases. The mean value of hypocalcemia was 1.69 mmol/l.

Etiologies included idiopathic hypoparathyroidism in 4 patients, pseudohypoparathyroidism in 5 cases, secondary hypoparathyroidism, isolated hypovitaminosis D and cerebral radiotherapy in one case for each and Fahr's disease in 4 patients. Oral calcium and vitamin D substitution were started in patients with parathyroid disturbances with favorable outcome.

Conclusion : In this report, we propose to discuss the clinical manifestations of FS, its etiologies especially parathyroid disturbances and its therapeutic modalities.

Key-words

Fahr's syndrome, hypocalcemia, hypoparathyroidism, pseudohypoprathyroidism.

Fahr's syndrome (FS) was first described by German neurologist Karl Theodor Fahr in 1930 (1). It is characterized by abnormal deposition of calcium in areas of the brain that control movements including basal ganglia (BG), thalamus, dentate nucleus, cerebellum, subcortical white matter and cerebral cortex. It typically affects individuals in the 3rd and 4th decades of their lives (2). This syndrome may present with different clinical aspects. It is mostly associated with a disorder of calcium and phosphate metabolism, especially due to parathyroid disturbances. However, it can also be attributed to infectious, metabolic, and genetic diseases.
The objective of this study is to ascertain epidemiological, clinical, etiological and therapeutic features of FS.

METHODS

We retrospectively reviewed the medical records of patients with FS attending the Department of Endocrinology at the Hedi Chaker University Hospital, Sfax, Tunisia, over a period of 16 years between January 1999 and 2014. For each case, we studied the demographic data (gender, age at onset, time to diagnosis), clinical features, treatment details, and the evolution. Laboratory findings including phosphate and calcium metabolism, vitamin D, magnesemia were obtained. Serum intact parathyroid hormone level was measured by radioimmunoassay (normal range between 15 and 68.3 pg / mL).
Hypovitaminosis D is defined as a 25(OH)D concentration less than 30 ng/mL. Vitamin D insufficiency is defined as a 25(OH)D concentration of 10 to 30 ng/mL. Vitamin D deficiency is defined as a 25(OH)D level less than 10 ng/mL. The diagnosis of hypoparathyroidism (HP) was made in the presence of hypocalcemia, hyperphosphataemia and a low PTH level. The idiopathic character of the hypoparthyroidism (IHP) was made in the absence of antecedent of thyroidectomy.
The combination of these same laboratory abnormalities with a normal or elevated PTH level allowed to retain the diagnosis of resistance syndrome to PTH or Pseudohypoparathyroidism (PHP). Biological and genetic explorations to classify subtypes of PHP were not performed. The diagnosis of Fahr disease was made in the absence of endocrine, infectious and autoimmune etiologies.

RESULTS

A total of 16 patients (12 men and 4 women) were included. The main clinical, biological findings, cerebral imaging and treatment of the patients are summarized in table 1.
The female to male sex ratio was of 1:3. The mean age was 44.68 years (11-67 years). In all patients, FS was revealed by neuropsychiatric symptoms.

Table 1: Epidemiological, clinical, laboratorial, treatment and evolution data in patients with Fahr's syndrome.

Patients	16
Mean age	44.68 years (11-67 years)
Sexe	12 M/ 4 F
Median delay to diagnosis of FS (months)	23.80
Main central neurological presenting features	
Seizures	6
Headaches	5
Parkinson's syndrome	3
Intracranial hypertension	1
Ischemic attack	1
Psychiatric disorders	2
Confusion	1
Facial paralysis	1
Dystonia	1
Clinical features of hypocalcemia	6
Calcification site	
Basal ganglia	16
Dentate nuclei	2
Cerebellum cortex	2
The thalami	3
The subcortical white matter	2
The brainstem and the cortico- subcortical junction	1
PTH	
High	6/14
Normal	4/14
Low	4/14
Diagnosis	
IHP	4
PHP	5
SHP	1
HVD	1
CR	1
FD	4
Treatment	
Calcium	10
Vitamin D substitution	10
Magnesium	2
Antiepileptic drugs	4
Antidepressant drugs	2
Levo-dopa therapy	3
Paracetamol	1
Outcome	
Favorable	10
Partial improvement	5
Death	1

The median delay to diagnosis was 23.8 months.
The most main presenting central neurological features were seizures in 6 cases including generalised tonic clonic seizures in 4 cases and partial seizures in 2 cases. Headaches were noted in 5 patients and parkinson's syndrome in 3 cases. Intracranial hypertension, confusion, vertigo, facial paralysis, dystonia, ischemic attack with dyarthria and pyramidal syndrome were found in one case for each. Psychiatric disorders were observed in 2 patients including memory loss and iritability.
Hypocalcemia clinical features were observed in 7 cases.

They preceded diagnosis of FS in 4 cases with a mean delay of 4.25 years. They postdated it in the others. Increases neuromuscular irritability symptoms included tetany in 3 cases, paresthesia in 4 cases, muscle cramp in 3 cases, obstetrician's hand in 2 cases and positive chvostek's and trousseau's signs in 3 cases. Prolongation of QT interval was noted in 2 cases, cataract in 4 cases, subcutaneous calcinosis in one case. Biological finding included hypocalcemia in 10 cases with a mean value of 1.69 mmol/l, hyperphosphatemia in 8 cases, hypocalciuria in 6 of 7 tested cases and hypomagnesemia in 2 cases. Hypovitaminosis D was noted in 4 of 5 tested with insufficiency in 2 cases and deficiency in the others.

Serum intact parathyroid hormone level was reduced in 4 of 14 tested, elevated in 6 of 14 and normal in 4 of 14.

FS was confirmed in all cases by Computed tomography (CT) scan of the brain.

The calcifications concerned BG in all cases (**figure 1, 2, 3**), the dentate nuclei and the cerebellum cortex (**figure 4**) in 2 cases for each, the thalami in 3 cases, the subcortical white matter (**figure 2, 5**) in 2 cases , the brainstem and the cortico- subcortical junction in one case.

Brain magnetic resonance imaging (MRI) was performed in one case showing hyper intensity T1 (**figure 6A**) and Flair T2 (**figure 6B**) in bilateral BG, thalami and subcortical white matter.

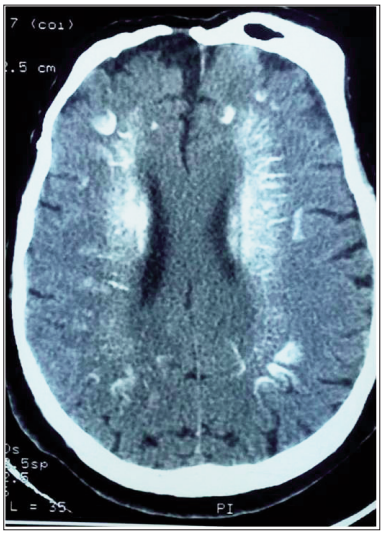

Figure 1: CT scan axial view demonstrating extensive bilateral calcifications in the BG and periventricular white matter.

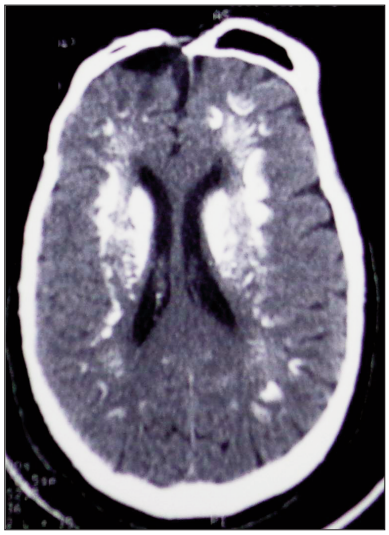

Figure 2: CT scan axial view demonstrating extensive bilateral calcifications in caudate nuclei, external capsule and subcortical white matter.

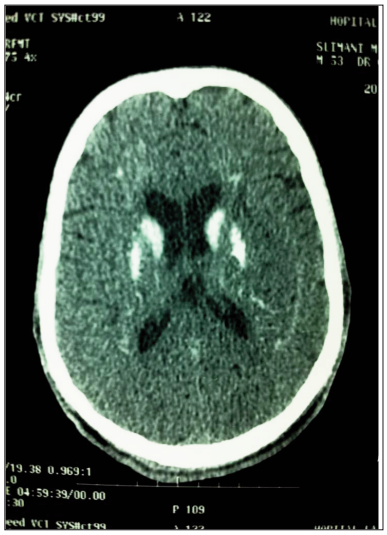

Figure 3: CT scan axial view demonstrating bilateral calcifications in caudate nuclei and putamen.

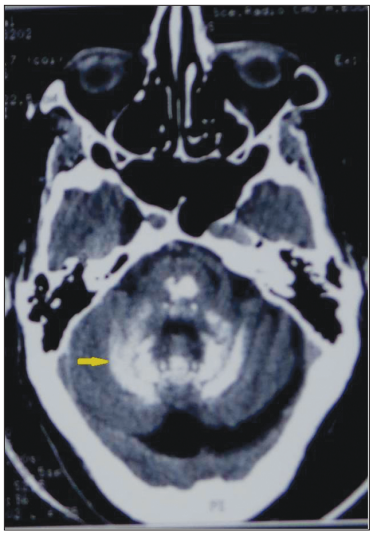

Figure 4: CT scan axial view demonstrating calcifications in both cerebellar hemispheres.

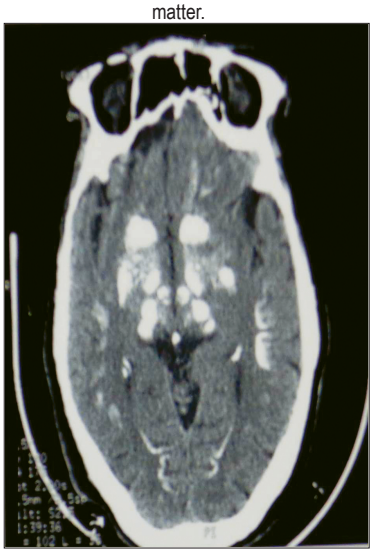

Figure 5: CT scan axial view demonstrating extensive bilateral calcifications in white matter

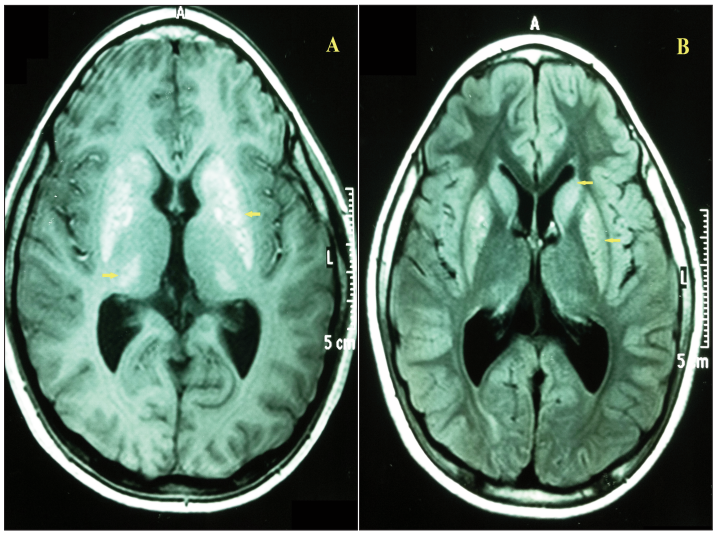

Figure 6: Brain magnetic resonance imaging (MRI) showing hyper intensity T1 (6A) and Flair T2 (6B) in bilateral BG and thalami.

Etiologies included idiopathic hypoparathyroidism in 4 cases, Pseudohypoparathyroidism in 5 cases, secondary hypoparathyroidism (SHP), isolated hypovitaminosis D, cerebral radiotherapy in one case for each and Fahr's disease in 4 cases.
Vitamin D substitution associated with oral calcium were started in 10 cases.
Symptomatic treatment included antiepileptic drugs in 5 cases, anti-depressant and levodopa therapy were used in 2 patients for each.
The majority of patients with parathyroid disturbances were notably improved with calcium and vitamin D therapy. The phosphate and calcium metabolism disorders were totally normalized. The intracranial hypertension had disappeared with calcium substitution and acetazolamide (Diamox*). Parkinson's syndrome and psychiatric features were partially improved in 2 cases for each. No recurrence of seizures was noted.

DISCUSSION

In this study, we report 16 cases of FS and describe their clinical features, etiologies and therapeutic modalities.
FS is defined by the presence of bilateral symmetrical striatopallidal calcifications at the base of the skull. Its etiopathogenesis remains largely obscure and continues to attract attention even now. Focal deposition of calcium in basal ganglia can be due in part to calcium metabolism disturbances (3).
FS may be associated with a broad spectrum of clinical features. About half of the patients with FS present neuropsychiatric manifestations. The most common neurological symptoms are headache, seizures (4,5,6), vertigo, extrapyramidal symptoms (4,7), movement disorders (4,7) such as dystonia and cerebellar ataxia, stroke like events (7), confusion (8,9), dementia and unconsciousness.
The psychiatric symptoms are also frequent in the onset of the disease ranging from anxiety (10) to psychosis. Among these, cognitive, behavioral [(7,11) and psychotic disorders (7, 12-15) are the most prominent.
In our report, the most frequent neurological features were seizures in 6 cases, headaches in 5 cases and parkinson's syndrome in 3 cases. Meanwhile, only 2 patients had FS presenting with psychiatric signs including memory loss and irritability.
Meanwhile, El Otmani H (4) had conducted a retrospective study including twelve patients with FS. Tetany was observed in all patients, seizures in 60%, associated in one patient with benign intracranial hypertension; extrapyramidal symptoms in 25 % including parkinson's syndrome in 2 cases and movement disorders in one case. Psychiatric disorders were more frequent than in our study including behavioral changes in 50 % and cognitive impairment in 25 %.
Most commonly, hypocalcemia may present with neuromuscular irritability, cardiovascular manifestations such as prolonged QT intervals, electrocardiographic changes that mimic myocardial infarction or heart failure. Ocular features can also be present such as cataract.
In some cases, it is difficult to precise if the neurological symptoms are related to reversible mineral disorders or irreversible intracerebral calcifications.
In our case series, hypocalcemia clinical features were present in 7 cases. The most frequent manifestations were paresthesia and cataract in 4 patients, tetany, muscle cramp and positive chvostek's and trousseau's signs in 3 cases for each.
The calcifications typically involve the BG. The most frequently affected area is the lenticular nucleus, especially the internal globus pallidus (2). Calcifications in the thalami, the dentate nuclei and the cerebellum are also common.
In our report, calcinosis involved the BG in all cases, the dentate nuclei and the cerebellum cortex in 2 cases for each, the thalami in 3 cases and the subcortical white matter in 2 cases. It exceeds the common brain locations and involves the brainstem and the cortico- subcortical junction in one case.
However, in the report of El Othmani (4), the dentate nuclei and the thalami were more involved than in our series with a frequency assessed at 60% and 40% of cases respectively.
Parathyroid disturbances are the most frequent endocrine disorders causing FS. These abnormalities include idiopathic hypoparathyroidism in 21.5 to 41.6 % of cases (4,16), secondary hypoparathyroidism in 15 % to 30 % (4,16,17,18) and pseudohypoparathyroidism in 25 to 42 % (2,4,6). Pseudo-pseudohypoparathyroidism and hyperparathyroidism are rarely described (9,19).
In our case series, the parathyroid disturbances were the most frequent etiologies of FS including IHP in 4 cases, PSHP in 5 cases and SHP in only one patient.
Goswani and al (20) reported the occurrence of BG calcifications in 73.8% in a large cohort of 152 patients with IHP. The occurrence and the progression of FS during follow-up were related to a low calcium/phosphorus ratio.
Vitamin D is a known player in the process of calcium metabolism. Its homeostasis disturbances have significant implications for patients with FS (2). Isolated hypovitaminosis D was noted in only one of our patients.
Besides endocrine disorders, FS may be due to mitochondrial myopathy (21), neurodegenerative conditions, Tuberous Sclerosis Complex and infectious diseases such as brucellosis (22). FS can be an incidental finding in about 0.3%-1.5% of brain CT scans, especially in elderly (2). In our study, FS was due to brain radiotherapy in one patient which is rarely reported (23).
About 25 % of our patients had idiopathic FS with a mean age of 59.25 years. Indeed, the FS can be idiopathic with sporadic or familial presentations. An autosomal dominant

pattern of inheritance is probably implicated. Three causative genes have been recently reported: SLC20A2, which encodes the inorganic phosphate transporter PiT2, PDGFRB which encodes the transmembrane receptor PDGFRb, and PDGFB, which encodes PDGF-B, the main ligand of PDGFRb (24).

The treatment of FS is directed to the identifiable cause. Neuropsychiatric symptoms which are related to the parathyroid disorders can be resolved with the correction of phosphate and calcium levels. The standard treatment of HP and PHP involves calcium and vitamin D supplementation.

Symptomatic treatments may be proposed on a case-by-case basis including anticonvulsants in seizures, levodopa therapy in parkinson's syndrome, antipsychotic and antidepressant drugs in psychiatric disorders.

In our report, Vitamin D substitution associated with oral calcium was started in 10 cases. Symptomatic treatment included antiepileptic, anti-depressant and levodopa therapy. Favorable outcome was noted in the majority of patients with parathyroid disorders. However, patients with Fahr disease presenting with psychiatric signs were partially improved.

El Othmani (4) suggested that epilepsy and psychiatric disorders in patients with HP are reversible after hypocalcemia correction. However, patients with PHP having extrapyramidal symptoms, cognitive impairment and extensive brain calcifications were not responsive to calcium therapy.

CONCLUSION

In the case of neuropsychiatric disorders, FD should be taken into consideration despite its rarety. Our report includes a great number of patients having this rare entity with a broad spectrum of clinical and etiological features. Parathyroid diseases were the most common causes of FS so that parathyroid analyses should be investigated in all patients with phosphate and calcium metabolism disturbances. Calcium and vitamin D supplementation can improve clinical symptoms and FS progression.

REFERENCES

1. Fahr T: Idiopathische verkalkung der hirngefässe. Zentrabl Allg Pathol 1930; 50:129–133.
2. Saleem S, Aslam HM, Anwar M et al. Fahr's syndrome: literature review of current evidence. Orphanet Journal of Rare Diseases 2013; 8:156.
3. Morgante L, Vita G, Meduri M et al. "Fahr's syndrome: local inflammatory factors in the pathogenesis of calcification". J Neurol 1986 ; 233(1):19-22.
4. El Otmani H, Lahlou I, Raji L et al. Striatopallidodentate calcinosis, hypoparathyroidism and neurological features: a case series study. Rev Neurol (Paris) 2013;169(6-7):495-501.
5. Guedes C, Macedo B. Fahr Syndrome. Acta Med Port 2013; 26(2):180-180.
6. Swami A, Kar G. Intracranial hemorrhage revealing pseudohypoparathyroidism as a cause of fahr syndrome. Case Rep Neurol Med 2011; 2011:407567.
7. Khammassi N, Chrifi J, Mohsen D, Abdelhedi H, Tougourti MN, Hamza M. Fahr's syndrome: Two case report. Rev Neurol (Paris) 2010 ;166(4):446-50.
8. Sbai H, Smail L , Hamdani S et al. Fahr syndrome discovered following a bacterial meningitis. Rev Med Interne 2008; 29(5):412-4.
9. Rharrabti S, Darouich I, Benbrahim M, Belahsen F, Rammouz I, Alouane R. A confusional syndrome revealing a Fahr syndrome with hyperparathyroidism. Pan Afr Med J 2013; 14:123.
10. Chevalier D, Marie I, Tillon J, Lévesque H. A cause of cerebral calcifications not to be ignored: Fahr syndrome. Rev Med Interne 2005; 26(8):668-70.
11. Lam JS, Fong SY, Yiu GC, Wing YK. Fahr's disease: a differential diagnosis of frontal lobe syndrome. Hong Kong Med J 2007;13(1):75-7.
12. Faye AD, Gawande S, Tadke R, Kirpekar VC, Bhave SH. A case of psychosis due to Fahr's syndrome and response to behavioral disturbances with risperidone and oxcarbazepine. Indian J Psychiatry 2014; 56(2):188-90.
13. El Hechmi S, Bouhlel S, Melki W, El Hechmi Z. Psychotic disorder induced by Fahr's syndrome: a case report. Encephale 2014; 40(3):271-5.
14. Shirahama M, Akiyoshi J, Ishitobi Y et al. A young woman with visual hallucinations, delusions of persecution and a history of performing arson with possible three-generation Fahr disease. Acta Psychiatr Scand 2010 ;121(1):75-7.
15. Otheman Y, Khalloufi H, Benhima I, Ouanass A. Neuropsychiatric symptoms revealing pseudohypoparathyroidism with Fahr's syndrome. Encephale 2011; 37(1):54-8.
16. Bruyn G, Bots G, Staal A: Familial bilateral vascular calcification in the central nervous system. Psychiatr Neurol Neurochir 1964; 67:342.
17. Zisimopoulou V, Siatouni A, Tsoukalos G, Tavernarakis A, Gatzonis S. Extensive bilateral intracranial calcifications: a case of iatrogenic hypoparathyroidism. Case Reports in Medicine 2013; 2013:932184.
18. Jorens PG, Appel BJ, Hilte FA, Mahler C, De Deyn PP. "Basal ganglia calcifications in postoperative hypoparathyroidism : A case with unusual characteristics," Acta Neurol Scand 1991; 83(2):137-40.
19. Ceccaldi B, el Maghraoui A, Mayaudon H, Dupuy O, Eulry F, Bauduceau B. Fahr syndrome and hyperparathyroidism. Presse Med 1999; 28(13):689.
20. Goswami R, Sharma R, Sreenivas V, Gupta N, Ganapathy A, Das S. Prevalence and progression of basal ganglia calcification and its pathogenic mechanism in patients with idiopathic hypoparathyroidism. Clin Endocrinol (Oxf) 2012 ; 77(2):200-206.
21. Etcharry-Bouyx F, Ceccaldi M, Poncet M, Pellissier JF. Fahr's disease and mitochondrial myopathy. Rev Neurol 1995; 151(12):731–733.
22. Mousa AM, Muhtaseb SA, Reddy RR, Senthilselvan A, Al-Mudallal DS, Marafie AA. The high rate of prevalence of CT-detected basal ganglia calcification in neuropsychiatric (CNS) brucellosis. Acta Neurol Scand 1987; 76(6):448–456.
23. Cavalcanti-Mendes Gde A, Carvalho GT, Christo PP, Malloy-Diniz LF, Sousa AA. An unusual case of Fahr's disease. Arq Neuropsiquiatr 2009; 67(2B):516-8.
24. Nicolas G, Richard AC, Pottier C and al. Overall mutational spectrum of SLC20A2, PDGFB and PDGFRB in idiopathic basal ganglia calcification. Neurogenetics 2014; 15(3):215-6.