The Fahr syndrome and the chronic lymphocytic thyroiditis

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Abstract
Fahr syndrome (FS) refers to basal ganglia calcification that is associated with many neurological and psychiatric abnormalities and appears as secondary to other diseases. We described a case of FS patient who was admitted in the Department of Neurology of “Prof. Dr. Nicolae Oblo” Clinical Emergency Hospital, Iassy, Romania, with seizure and mood disorders. On CT, the cause of seizure was found to be the bilateral calcifications of cerebellum, basal ganglia, thalamus and internal capsule. As the patient died after 15 days of hospitalization due to new seizures and gastrointestinal infection, an autopsy was made. Grossly, there were bilateral symmetrically gritty yellow areas in basal ganglia, thalami, internal capsule, cerebral cortex, cerebellar folia, dentate nucleus, and brain stem. A detailed histopathological examination revealed five types of calcium deposits within the walls of capillaries, small and medium-sized arteries from the intracerebral affected areas, chronic lymphocytic thyroiditis and fibro-adipose tissue instead of parathyroids. We consider that intracerebral symmetrical calcifications were the results of the hypoparathyroidism determined by an ancient autoimmune parathyroiditis that evolved to fibrosis as at microscopy we found an autoimmune thyroiditis.

Keywords: Fahr syndrome, chronic lymphocytic thyroiditis, autopsy, symmetrical bilateral intracerebral calcification.

Introduction
The Fahr syndrome is a degenerative neurological disorder whose prevalence is probably less than 0.5%. This condition is characterized by the presence of bilateral intracranial calcifications with predilection for the basal ganglia and dentate nuclei and is associated with disturbances of calcium and phosphorus metabolism [1–3]. The calcifications of vessels in basal ganglia have been described since 1850 when Delacour [4] presented a patient of 56-year-old who showed tremor, stiffness, weakness and lower extremity vascular calcification of the basal ganglia. In 1855, Bamberger presented the histopathological aspects of this type of calcification in autopsy of a woman with mental retardation and seizures [5]. Almost a century later, in 1930, the calcifications of the basal ganglia named “Fahr’s disease”, after the German neuropathologist Karl Theodor Fahr, although he presented a 55-year-old patient with a history of dementia and hypothyroidism, with the “immobility without paralysis” but the histopathological aspects of “rough granular cortex and calcifications in centrum semiovale and striatum” and not in the basal ganglia [5–7].

Since then, the literature uses the Fahr syndrome (FS) term, which was applied to basal ganglia calcifications regardless of etiology, but associated with low serum levels of calcium and phosphorus, which usually occur in hypoparathyroidism and the name of Fahr disease is used for primary basal ganglia calcification, although idiopathic, sometimes in the family without a known cause, the calcium deposit is made on previous deposits of mucopolysaccharides [1, 8–10]. Both entities are defined by bilateral intracranial calcification with neuropsychiatric symptoms and extrapyramidal disorder [11]. In both cases, the appearing granular deposits of free calcospherits or in the vessel walls in the nervous tissue [10].

In this study, we present the macroscopic and microscopic aspects of a case with autopsy findings in Fahr syndrome and discuss the etiopathogenesis of this condition.

Patient, Methods and Results
A 68-year-old female patient was admitted in the Department of Neurology of “Prof. Dr. Nicolae Oblo” Clinical Emergency Hospital, Iassy, Romania, with new onset generalized tonic-clonic seizures. She was known
for 23 years as having episodes of grand-mal seizures. She was treated as a case of status epilepticus with Carbamazepine. During the hospitalization, detailed examination revealed postural static tremor of upper limbs, cogwheel rigidity, more pronounced on right side, mild muscular hypertonia, positive Babinski sign on the left, dystonic and choreoathetoid movements of upper limbs. The psychological examination revealed a depressive disorder on a dispositional background of overall deterioration. General examination revealed an anemic syndrome, ischemic chronic cardiopathy and hypothyroidism. X-ray showed pulmonary fibrosis. She was treated for a cerebral infarct one year before. Ophthalmologic examination showed partial optic atrophy of both eyes. Laboratory studies revealed obvious anemic syndrome (Hb 9.8, Ht 30%, erythrocytes 3 250 000/mm³). The sedimentation blood rate was 85 mm/h. Cholesterol 210 mg/mL, lipids 65 mg/mL, triglycerides 88 mg/mL. The urinary sediment showed the presence of traces of albumin and amorphous phosphates. Hormonal examination of the parathyroid gland, serum calcium and phosphorus was not performed.

A non-contrast CT scan head revealed bilaterally symmetrical hyperdense lesions of calcification, located infra- and supratentorial, involving brainstem, cerebellar hemispheres, globus pallidus, putamen, caudate nucleus, thalami, periventricular and semi-oval centre (Figures 1 and 2).

Magnetic resonance imaging showed extensive surfaces of T2 hypersignal and Flair on the periventricular white substance and on the semi-oval centre which were interpreted as suggestive images of degenerative cerebral vascular disease as well as T1 and T2 hyposignal images of about 1 cm, located in the right occipital horn (possibly calcification) and small lesions in T2 hypersignal and Flair located symmetrically and paramedian in the cerebellar lobes and in the brainstem deck.

The patient received antiepileptic treatment (Carbamazepine), but seizures reappeared. The patient became febrile due to bronchopneumonia and gastrointestinal infection and died in two days.

An autopsy was made. Brain showed diffuse atrophy (weight 900 g). Grossly, after multiple coronal sections, the brain showed bilateral symmetrical gritty and yellow areas in globus pallidus, putamen, thalamus, hypothalamus, semi-oval centre, cerebral cortex, cerebellar cortex, dentate nuclei, pons and medulla oblongata. In the right occipital lobe and in left cerebellar hemisphere, one cystic area filled with a colorless liquid was observed. The thyroid gland enlarged and contained numerous colloid cysts while the parathyroid glands could not be identified, being replaced by a conjunctive-adipose tissue. The heart had small pearly white areas of fibrosis in the interventricular septum. On sectioning, both lungs showed small yellowish nodular formations, slightly raised and separated by relatively normal lung tissue. The small intestine and the colon had blackish-red wall with gray-yellowish free running mucus lining it. The liver had a slightly increased volume and had a yellowish color. The kidneys showed numerous areas retracted on the external surface. The adrenal glands showed post mortem autolysis.

Samples of brain and other organs were taken. Tissues were fixed in 10% buffered formalin, and paraffin sections were made. Sections were stained with Hematoxylin and Eosin (HE).

Light microscopic examination revealed various degrees of granular basophilic material (calcium deposits) in the vessels walls of the nervous tissue. The calcification always occurred bilaterally, in cerebral cortex, semi-oval centre, caudate nucleus, globus pallidus, thalami, hypothalamus, cerebellar cortex, dentate nucleus, pons and medulla oblongata.

The calcification occurred in five clearly differentiated patterns varying in shape and size:

- Type 1: Fine basophil granules looking like "strings of pearls", located in the walls of capillaries (Figure 3);
- Type 2: Larger, irregular limestone deposits, randomly arranged in small vessel walls (Figure 4);
- Type 3: Basophilic concentric lamellar structures located in the tunica media of small and medium vessels leading to obvious thickening and narrowing of the vascular lumen (Figure 5);
- Type 4: Massive calcium deposits in artery walls with appearance of ossification in the walls of small and medium-sized arterial walls (Figure 6);
- Type 5: Spherical limestone concretions of various sizes located in the nervous parenchyma, apparently unrelated to a blood vessel (Figures 7 and 8).

The white substance showed diffuse reactive gliosis more obvious around the larger calcium deposits while in the gray substance areas a nerve cell loss was found, the remaining neurons having a pyknotic nucleus and an intense eosinophilic cytoplasm.

In the neurohypophysis, only one vessel was identified having a massive presence of concentric calcification in the wall and a massive reduction of the lumen (calcification Type 4).
The thyroid had large follicles filled with weak eosinophilic colloid. In some areas, in the thyroid stroma, small lymphocytic conglomerates were observed sometimes centered by small thyroid follicles with necrosis of thyroid follicular cells (Figure 9).

Figure 3 – Cerebral cortex: finely granular or coarse calcium deposits, arranged as “strings of pearls” in the walls of capillaries (calcification Type 1), the number of nearby neurons is reduced visible (HE stain, ×200).

Figure 4 – Globus pallidus: segmentary deposits of basophilic material (calcium) in the wall of a small artery (calcification Type 2) with marked reduction of the surrounding neurons (HE stain, ×100).

Figure 5 – Dentate nucleus (cerebellum) lamellar massive calcification in the walls of small arteries (calcification Type 3) (HE stain, ×40).

Figure 6 – Globus pallidus: massive calcification in the walls of small vessels with marked reduction in lumen (calcification Type 3), reducing number of surrounding neurons, the remaining ones taking a pyknotic appearance (HE stain, ×200).

Figure 7 – Cerebellar white substance: massive calcium deposit with an aspect of ossification (calcification Type 4) in the arterial wall of a small vessel (HE stain, ×100).

Figure 8 – Cerebellar cortex: amorphous calcifications masses with an aspect of “limestone concretions” (calcification Type 5) in the granular layer, formed by evolution towards the conglomeration of small original limestone deposits (HE stain, ×200).
The parathyroids could not be identified, only a conjunctive-adipose tissue being visible in those areas. The heart presented widespread fibrosis replacing the myocardial fibers. The lungs showed acute suppurative exudates (neutrophils) in the alveolar lumen and bronchiole. Kidneys showed tubular necrosis with eosinophilic material in the tubular lumen. In the small intestine adventitia several small vessels basophilic deposits were detected in the walls. The epithelium of the small intestine had ulcers covered by fibrin while in the neighborhood polymorphic inflammatory infiltrates were observed, predominantly lymphocytic in the epithelium and lamina propria.

The final pathological diagnosis included the following: multiple cerebral and cerebellar infarcts, Fahr’s cerebral calcification, chronic lymphocytic thyroiditis, myocardial ischemic fibrosis, bronchopneumonia, enterocolitis.

Discussion

The Fahr syndrome (FS) defines over 30 conditions that result in metastatic or bilateral dystrophic calcification in the basal ganglia and can be classified as inflammatory (CMV infection, neurocysticercosis, toxoplasmosis, neurobrucellosis, tuberculosis, HIV infection), tumoral (astrocytomas), hypoxic and vascular (arteriovenous malformations, calcified infarct, ischemic encephalopathy), endocrinal (hypoparathyroidism, pseudohypoparathyroidism, hyperparathyroidism), toxic (CO and Pb intoxication, hypervitaminosis D, radiotherapy), metabolic and degenerative (senility, mitochondrial encephalopathies, leukodystrophic diseases, idiopathic familial, motor neuron disease, mytonic muscular dystrophy, carbonic anhydrase deficit, biotinidin deficit) and other (malabsorption, Down syndrome, lupus, tuberous sclerosis, arthrogriposis) [7, 12, 13].

Lowenthal (1986) established the defining criteria to the Fahr syndrome (including Fahr disease): (1) Calcifications should have a characteristic distribution, or to inquire at least globus pallidus, with or without cerebellar calcification; (2) The calcifications should be obvious on the computed tomography; (3) The calcifications should be large enough to be detected at macroscopic examination. Aspects that support this diagnosis, but are non-diagnostic, include the following: (1) Determinable clinical presentation, and (2) Existence of a metabolic abnormality, particularly hypoparathyroidism [14].

The onset age of clinical symptoms is usually between 30–60 years [15, 16]. Fahr syndrome patients (including those with Fahr disease) may exhibit movement disorders such as Parkinsonism, chorea, tremor, paresis, dystonia, speech disorders [1, 2, 11]. Other neurological symptoms may include events such as stroke, seizures, syncope, often associated with psychiatric conditions such as psychosis or dementia [9, 15, 16].

The Fahr syndrome diagnosis in this case was based on clinical data (disease onset at the age of 45 years; the disease initially manifested by episodes of grand mal seizures, which were later associated with other neurological and psychiatric symptoms) imagistic aspects (bilateral intracerebral calcifications in almost all the intracranial nerve structures) and autopsy aspects (atrophic brain that weighed only 900 g, bilateral calcification of various sizes and shapes, located in the walls of capillaries, small and medium arteries of all intracranial nerve structures). There could not be determined the serum levels of calcium, phosphorus, alkaline phosphatase and of the parathyroid hormone.

The most common area of calcification in Fahr disease is globus pallidus, but the Fahr syndrome also involves other intracerebral areas that may include putamen, caudate nucleus, dentate nucleus, lateral thalamus (striopallidodentate calcification) and cerebral cortex, internal capsule, cerebellar film [13, 17–19]. This pattern of arrangement of bilateral intracerebral calcifications was also identified in our case as the computed tomography and magnetic resonance imaging revealed symmetrical and extensive calcifications in the putamen, globus pallidus, caudate, dentate nucleus, thalamus, cortex, cerebellum and internal capsule. The microscopic examination confirmed postmortem vascular calcifications in all these areas, but also in the brainstem situation, which is rarely reported in other studies [20].

Neuropathological studies have shown that intracerebral bilateral mineral deposits are composed of non-atherosclerotic calcium located in the walls of small vessels, especially those in areas that control movement [5]. Those patients with dementia show evidence of neuronal loss in the fronto-temporal cortex and in the basal nucleus of Meynert. The calcifications affecting the average of small and medium arteries and the perivascular tissue of arterioles and capillaries are associated with neuronal degeneration and gliosis [21].

Fujita D et al. have classified how calcium deposits are made on intracerebral vessel walls into three patterns: diffuse deposition within the tunica media of small and medium-sized vessels (Type 1 deposition), free spherical or lobulated concretions (Type 2 deposition) in the parenchyma, and rows of small calcospherites lying along capillaries (Type 3 deposition) [22]. The detailed histological examination of those sections taken from the affected areas in this case we have shown that calcium
deposits are present in all intracranial nerve structures and that they can take five morphological aspects, from early lesions to ossification and concretion images. These morphological aspects may suggest the evolutionary picture of Fahr type dystrophic calcification and at the same time, they explain the polymorphism of clinical manifestations. The initial calcification vessel walls showed thickening by means of a homogeneous material, slightly eosinophilic, possibly a degenerative protein substance that allows the initiation of calcification, followed by a slowly progressive deposit of calcium and probably other minerals, possibly related to the metabolic disturbance of calcium/phosphate. Our study also demonstrated that along with the calcium deposits identified in various forms and degrees in the walls of capillaries and small and medium arteries, the nervous tissue develops an important reactive gliosis and a significant reduction of the number of neurons in the corresponding areas, probably due to a progressive decrease of the corresponding blood flow.

Several researchers have investigated the mineral elements shown in the vascular calcifications in the Fahr syndrome and proposed the term “mineralization” for these deposits since it has been shown that they contain, apart from calcium, a wide range of other minerals: P, Fe, Cl, S, Al, K, and Zn [23, 24].

The pathophysiology of the Fahr syndrome is still unknown, but there are hypotheses that the intracerebral calcium deposit is a metastatic type, secondary to local disruption of blood-brain barrier being or to a calcium neuronal metabolism disorder [15]. Other authors have found that a defective transport of iron or increased production of free radicals may be possible factors to initiate calcification [16].

Recent allegations sustain that the bilateral basal ganglia calcifications may be the result of a latent viral infection, possibly with Epstein–Barr virus (EB). Morishima T et al. (2002) analyzed the lymphocyte subsets and the cytokines in the peripheral blood of 10 adults with calcification of the basal ganglia concluding that the natural killer cells which release cytokines in the circulation, particularly the tumor necrosis factor-α, may be involved in the pathophysiology of this syndrome and that the EB virus and other viruses may be associated with the etiology of basal ganglia calcifications [25].

Apart from the family cases, considered to be genetically determined, such as Fahr disease, the accumulation of calcium in Fahr syndrome is due to the abnormal seric levels of this mineral (associated with changes in vascular permeability due to local calcium concentration) or to the dystrophic calcifications associated with local circulatory disturbances and metabolic disorders (hypoxia, hypoglycemia, disorders of fluid and electrolyte balance) [12].

Vega MG et al. demonstrated the correlation between the bilateral basal ganglia calcification, hypoparathyroidism and extrapyramidal syndrome [26]. Morgante L et al. reported three cases of Fahr’s syndrome with disorders of calcium metabolism and had had meningocerephalitis during their childhood. They hypothesized that gliovascular changes caused by cerebral inflammation may facilitate the emergence of calcifications within the striopallidodentate system when there is a disruption of the calcium metabolism [27].

The pathophysiological mechanism of calcification in Fahr syndrome is also discussed by Guseo A et al. who stress the role of increased permeability and the dysfunction of mesenchymal cells in the vessel walls [19]. Somehow, the same hypothesis is also issued by Kobayashi S et al. who, by means of transmission electron microscopy, revealed small deposits, especially in the adventitious cells cytoplasm of the blood vessels and sometimes by means of cytoplasmic processes of the glial cells, which led the researchers to believe that the pericytes could play an important role in the onset of calcification in Fahr’s syndrome [23].

The etiopathogenesis of symmetric intracerebral calcifications and of multiorgan calcifications (neurohypophysis, thyroid, small intestine) identified in the presented case still remains uncertain. However, some speculations are possible. Our case presented a chronic lymphocytic thyroiditis. Patients with autoimmune endocrine disease are at increased risk of developing other autoimmune diseases, both in the other endocrine glands and the other non-endocrine organ, which is defined as the polyglandular autoimmune syndrome. Autoimmune hypoparathyroidism and autoimmune thyroid disorders are included in the autoimmune polyglandular syndrome [28], which was classified into four types according to the affected organs [29]. From a histopathological point of view, the glands affected by this syndrome present in their structure mononuclear infiltrates consisting mainly of lymphocytes that are located in glandular stroma, but aggressing the parenchyma and leading to cell necrosis. As the disease progresses, atrophy and fibrosis install [30, 31].

In this case, although there are no neuroendocrinology or calcemia and phosphate investigations, given the presence of chronic lymphocytic thyroiditis, one can advance the hypothesis that autoimmune hypoparathyroidism is a possible cause of extensive symmetrical intracerebral calcifications. This hypothesis is supported by the fact that at autopsy, in the location of the parathyroid glands only fibro-adipose tissue was found, suggesting an ancient autoimmune pathology of the parathyroid glands. A similar situation was reported by Mori K et al., in 1991, but the hypoparathyroidism associated to the chronic thyroiditis was considered to be idiopathic [32].

Conclusions

Due to severe complications of hypoparathyroidism, especially significant being the extensive intracerebral calcification leading to neuropsychiatric symptoms resistant to treatment, it is important that in the presence of hypothyroidism determined by chronic lymphocytic thyroiditis, doctors should also consider the investigation of the parathyroid glands.

References


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