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Mineralization of the basal ganglia as the supposed cause of poor tolerance of zucloperthixol in a patient with long-term untreated paranoid schizophrenia

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Summary

Formations described as intracranial calcifications can appear in the course of diseases of the central nervous system, other systems and organs (e.g. endocrine), but also as a disorder of idiopathic character. They frequently locate in subcortical nuclei and usually constitute an incidental finding. This report presents the case of a patient suffering from paranoid schizophrenia for approximately 40 years, who did not agree to any treatment and was hospitalized against her will because she was the threat to the lives of others. She was treated with zucloperthixol resulting in positive symptoms reduction and considerable improvement in social functioning. Unfortunately neurological symptoms appeared: bradykinesia, rigidity - of the type of the lead pipe, balance, posture and gait abnormalities, disturbances in precise hands movements, double-sided Rossolimo's sign, plantar reflex without the participation of the big toe on the left. Neuroimaging studies have demonstrated changes in the form of lenticular nuclei calcification and reduction in signal intensity in the posterior parts of both putamens. Neurological symptoms decreased significantly after switching to atypical neuroleptic (olanzapine), and the patient did not require any additional treatment. Mineralization of the basal ganglia can often be associated with psychiatric disorders and it shouldn't be neglected it often requires modification of pharmacotherapy or additional neurological treatment.

Key words: basal ganglia, mineralization, calcification, Fahr's disease, schizophrenia

Introduction

Structures called intracranial calcifications can appear in course of diseases of the central nervous system, other systems and organs (e.g. endocrine), but also as a disorder of idiopathic character. They frequently locate in subcortical nuclei. Idiopathic cases are usually called Fahr's Syndrome (FS) or Fahr's Disease, after the name of

the author of the description dated 1930 [1]. Since 1999 FS is considered as a disease inherited in an autosomal dominant manner. It is associated with 14q chromosome, specifically the region called IBGC1 which is an abbreviation of name of the disease (*idiopathic basal ganglia calcification*) [2]. Other loci and also heterogeneity of this condition cannot be excluded, especially in isolated cases [3]. FS has been the subject of many case reports published also in Polish (5 reports concerning 7 cases) [4-8]. They include very detailed description of the disease and for that reason we will focus on ambiguities concerning the term FS.

Both terms: Fahr's Syndrome and Idiopathic Basal Ganglia Calcification IBGC (idiopathic meaning non-atherosclerotic) are not precise. Casanova and Araque consider this problem in their detailed review. Starting with the term Fahr's Syndrome – Karl Theodor Fahr described the case of 55 year old male with idiopathic calcification of vascular brain structures (...) „The patient complained of diarrhea, double vision, dizziness, and weakness and stiffness of the legs. His jaws were firmly locked and his thorax was strongly arched. After the hospitalization Fahr noted that his patient had tremors, hand cramps and „eclampsia-like” attacks. Postmortem microscopic examination revealed massive calcifications of small and medium size brain vessels, mostly in the white matter with only traces in basal ganglia”. [1 cited by 9].

The main concerns about the term FS are:

- K. T. Fahr was not the first who described the condition, what he mentioned himself. Few reports on BGC were published before 1930. The first one by Delacour followed by Virchow, Flesching, Perusini, Greenfield, Durk, Geyelin, Panfield and Ostertag; Misleading conceptions concerning BGC also appeared. Pick (1903) for instance, falsely assumed that calcifications in basal ganglia lead to tetany.
- Fahr's report mentioned calcifications in white matter (sic!) and only traces of it in basal ganglia;
- The clinical description does not quite correspond to extrapyramidal symptoms

Searching for articles in PubMed shows that this term is used for idiopathic (isolated, inherited) cases but also, for secondary processes appearing in course of hypoparathyroidism or Down Syndrome what causes terminological chaos. Casanova and Araque mention 13 synonyms of the term FS.

Further discrepancies concern histopathologic and pathophysiologic aspects (similarly 11 different terms) – what „calcium deposits” or „basal ganglia calcification” actually mean?

- Apart from organic compounds the deposits include many minerals. Mostly calcium and ferrum, but also zinc, copper, magnesium, aluminium and potassium
- The sequence of accumulation is unknown
- It is suggested that deposits composed mostly (sometimes even only) of ferrum are more pronounced in basal ganglia and they „clear the way” for calcium accumulation: this hypothesis could explain why basal ganglia constitute the most frequent localization of calcium deposits in the brain. Ferrum is a cofactor for

tyrosine hydroxylase so it should be present in dopamine-related regions of the brain like basal ganglia.

The clinical picture often includes psychiatric disorders, especially psychotic, affective, obsessive-compulsive, hallucinosis, medication dependence, personality disorders and most common, reaching 40% – cognitive deficits [7, 10, 11, 12]. Some reports describe schizophrenia-like symptoms [13]. The common feature is variability of psychiatric symptoms, mostly (besides inherited cases) incidental diagnosis and benign course of the illness.

Case report

75 year old female with no serious somatic problems, widow, living alone, rarely in contact with her family. She was diagnosed with paranoid schizophrenia approximately 40 years ago. The patient was admitted to the psychiatry department against her will. Her neighbors were alarmed by her aggressive behavior and suspected that she could cause an explosion because she was manipulating the gas-meter. The patient was hospitalized once before in her life, about 40 years ago, she destroyed the discharge card and did not tell anyone about being in hospital. She used medications incidentally, mostly did not agree to pharmacotherapy.

At admission she performed severe positive symptoms: delusions of reference, of control and persecutory, thought broadcasting and auditory hallucinations. Her affect was blunted, her mood was dysphoric, she had absolutely no insight. The patient was convinced that she had an electronic chip in her body and other people controlled her „mind machine” from outside. Psychotic symptoms caused actions like sending letters to investigative authorities about her being controlled-by external force, she almost wrote to European Court of Human Rights in Strasburg. During first days of hospitalization she assumed that people working at the department and also students shared her opinion about being investigated and when she was told it was not true, she started perceiving them as enemies.

The patient was given zuclopentixol, first in short acting injections, than in tablets and finally as a depot injection in maximal dose of 200 mg. This pharmacotherapy made her less irritated, positive symptoms considerably declined, but dissimulation could not be excluded. Additionally her delusions were supported by the patient’s rights representative, who helped the patient with writing to mentioned authorities. Above all, the patient cooperated and after some time she was allowed to leave the hospital for a few days. She kept a distance with the personnel, but was not hostile. Her condition would be satisfactory if it wasn’t for neurological symptoms.

Neurological examination revealed facial amimia, rare blinking, psychomotor retardation, lead-pipe rigidity, disturbances of the posture and walking (bent forward, shuffling, short steps) disturbed precise hand movements, double sided Rossolimo’s sign, plantar reflex without the participation of the big toe on the left.

Laboratory tests were done to exclude conditions like hypoparathyroidism, thyroid dysfunctions, renal failure. The results of creatinine, urea, uric acid, ASPAT, ALAT, bilirubin, sodium, potassium were normal; total cholesterol – 259,9 mg/dl, triglycerides

247,2 mg/dl, TSH, fT3 and fT4 were normal, total and ionized calcium, phosphorane, parathormone, FALK, copper and celuroplasmine levels were also normal. Electroencephalography did not reveal any pathology.

Computed tomography showed bilateral striatal calcifications of basal ganglia and moderately pronounced atrophy of frontal and temporal lobes with mild dilatation of ventricles corresponding to the size of atrophy (Tab. 1, 2).

Fig. 1. Brain CT scan. Bilateral streaky calcifications of basal ganglia. Mild cortical atrophy of frontal and temporal lobes



Fig. 2. Brain CT scan. Calcifications within basal nuclei. Ventricle system is symmetrical, not displaced but mildly extended according to the atrophy



Brain MRI which was performed 2 months later confirmed the above findings, but also demonstrated lenticular nuclei calcification and signal intensity reduction in posterior regions of both putamens in T2 and PD weighted images, what could be the result of calcium and ferritine accumulation in these regions (Tab. 3, 4).

Fig. 3. Brain MRI (FLAIR). Decrease of signal intensity within posterior parts of putamen, bilaterally, which can be related to calcium and ferritine accumulation within those structure. Cortical and sub-cortical atrophy of frontal and temporal lobes of both hemispheres

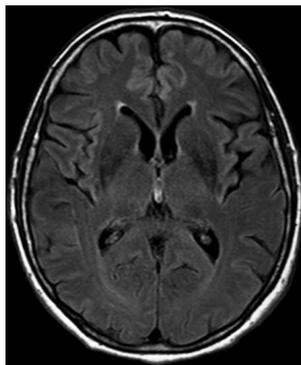
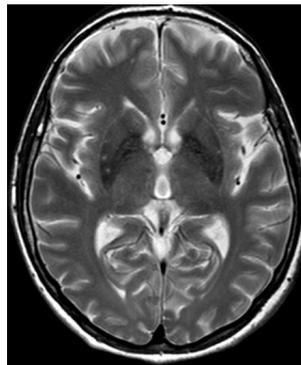


Fig. 4. Brain MRI (T2TSE). Linear calcification within medial parts of both lentiform nuclei. Significant decrease of signal intensity within posterior parts of putamen, bilaterally



Psychological evaluation: (Benton's visual memory test, Auditory Verbal Learning Test – AVLT, subtest from WAIS – R (PL): digit symbol, similarities) showed decreased short memory abilities, while repeating 5 elements sequence). Remembering words that were learned was also disturbed (curved line of learning) In the test exploring ability to create abstract notion the result was above average. Ability to focus attention was in lower limit of normal. Results of psychological tests may indicate malfunctions in central nervous system (confirmed by digit symbol test and qualitative analysis of Benton's visual memory test).

Regarding neurological symptoms, typical neuroleptic agent was exchanged to atypical one – olanzapine in dose of 10 mg and this modification alleviated neurological symptoms to the point where no additional pharmacotherapy was needed. Considering that the patient did not want to take any medication for 40 years and tolerate olanzapine very well, depot formulation was implemented (Zypadhera) 150mg every 4 weeks). Almost 12 months of observation after discharge confirmed her stable mental state.

Discussion

It is difficult to establish the exact course of disease. Information from patient's family was very scarce and beside admission time patient's relatives did not want to communicate with the doctors from the Clinic. However her family confirmed that the patient was diagnosed with schizophrenia about 40 years ago. The clinical picture on admission was in line with the diagnosis. Estimation of the time course of basal ganglia mineralization was not possible. Neurological examination revealed severe hypokinetic - hypertonic extrapyramidal syndrome and traces of pyramidal symptoms. Coexistence of both can indicate the beginning of degenerative process. Cognitive impairment, confirmed by psychological examination could support this diagnosis. Diagnosis of schizophrenia with coexisting FS is highly probable in this case although still hypothetical. Another possible coexisting condition is the beginning of degenerative process.

Extrapyramidal system dysfunctions result in various clinical pictures which makes diagnosis difficult. Caranci et al emphasize this problem in recently published report of four cases of basal ganglia calcification, two of which were diagnosed with FS and other two had hypoparathyroidism. Neuroimaging showed calcifications in similar regions of the brain, but clinical picture varied from hypokinetic parkinsonian-like syndrome to hyperkinetic syndromes [14]. Other authors like Maghraoui et al [15] also point this out.

Manyam et al analysed 99 cases (38 were his own observations and 61 were case reports) and concluded that the most common neurological manifestation of the disease were extrapyramidal symptoms like parkinsonian syndrome, athetotic and choreatic movements [11].

Psychiatric symptoms like decreased cognitive functions, personality changes, symptoms of depression, anxiety and psychotic disorders can also appear in course of basal ganglia mineralisation. Dogan et al recently described the case of a 53 year old patient, with FS, who experienced mainly memory decline and behavior disorder. The

authors emphasize that neuroleptic drugs should be used very carefully because the risk of evoking extrapyramidal symptoms in these patients is high [16]. It is suggested that the course of mineralization of basal ganglia is considerably benign [17, 18].

Considering controversies concerning the term „Fahr Syndrome” in sense of a distinct medical condition, as well as the fact that many reports were already published it might seem pointless to write another one. Nonetheless we assumed it is an important subject for two reasons:

Mineralization of basal ganglia is often associated with psychiatric disorders and this diagnosis should be considered especially in cases of psychotic symptoms appearing in patients with Down Syndrome [14, 19], cases of schizophrenia with oversensitiveness to neuroleptic agent [13, 20, 21], levodopa resistant extrapyramidal syndromes in course of Parkinson’s Disease and Parkinsonism Plus Syndromes like Multiple System Atrophy [20].

Recognizing this condition acquires treatment modification and sometimes additional pharmacotherapy

The finding of deposits in basal ganglia explained why the patient did not tolerate classical neuroleptic well and it was a sufficient reason to use olanzapine off label (Zypadhera is not recommended in patients over 75 years of age, because of increased risk of cerebro-vascular incidents). In this case of extrapyramidal system dysfunction it turned out to be a good choice. After this treatment modification patient did not require any neurological treatment. The impairment of cognitive functions was also mild and did not disturb patient’s everyday life.

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