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Familial neurodegenerative disease with parkinsonism and amyotrophic lateral sclerosis

The concurrence of amyotrophic lateral sclerosis (ALS) with parkinsonism syndrome and dementia is described as Guam ALS, in which up to 70% of patients have a positive family history.
The concurrence of parkinsonism with other neurological disorders, such as autonomic failure, dementia, cerebellar ataxia, visual disturbances, and pyramidal syndrome, is characteristic of some neurodegenerative diseases, for example, multiple system atrophy, dementia with Lewy bodies, progressive supranuclear palsy, and corticobasal degeneration. These diseases are common in the practice of a neurologist, have a detailed description and clear diagnostic criteria.
The isolated concurrence of parkinsonism and ALS without other neurological disorders is extremely rare. This disorder is known as Brait–Fahn–Schwartz disease and is named after the scientists who first described this overlap syndrome.
No cases of familial neurodegenerative disease concurrent with parkinsonism and ALS have been found in the literature. This paper presents the authors' own case of two siblings, one of whom is observed to have parkinsonism with ALS syndrome; and the other had Parkinson's disease.

Keywords: *parkinsonism; Parkinson's disease; Guam amyotrophic lateral sclerosis; electromyography; transcranial magnetic stimulation; Brait–Fahn–Schwartz disease.*
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We observed two sisters without a family history of neurodegenerative diseases, though their maternal grandmother in her later life was suffering from progressive weakness of the lower limbs; she died at the age of 76 (the cause of death is unknown) (Fig 1).

Case report 1. ***Patient M.****, 62 years old, was first admitted to Republican Hospital of Sakha (Yakutia) in August 2016 with complaints of tremor in both legs at rest which was exacerbated by anxiety and physical exertion, and disappeared during sleep and motion. She also complained of stiffness of the limbs, slow movements, shuffling gait, and thinness of the arms and legs. In January 2016 she first noticed weakness in her arms; in April she began experiencing tremor in her right leg at rest which quickly spread to the opposite side. Gradually, she developed rigidity and slowness of movements and shuffling. On examination she was found to have moderate oligobradykinesia, muscle rigidity (more pronounced on the right), leg tremor of medium amplitude at rest (mostly right-sided), acheirokinesis, shuffling, narrow gait, slouching posture, increased tendon and periosteal reflexes with anisoreflexia on the right, Babinsky sign on both sides, muscle hypotrophy of the forearms and hands (more pronounced on the left), hypotrophy of the peroneal muscles, rare fasciculations of the back muscles.*

In the inpatient department she was treated with dopamine receptor agonist pramipexole (with dose titration). The patient's gait improved and tremor decreased. She was discharged from hospital, and further dose titration of pramipexole up to 3 mg/ day was recommended.

The patient was re-examined after 1.5 years. She did not report worsening of her health status while taking pramipexole, and was able to cope with daily activities by herself. Neurological examination showed increased hypotrophy of the sternocleidomastoid muscle on the left side, more frequent fasciculations of the back and shoulder muscles, development of tetraparesis (in the upper limb muscles the force decreased proximally in the abductor and adductor shoulder muscles to 4 points; in the lower limb muscles – proximally to 3 points, distally to 4 points); appearance of other pathological signs (Schaefer's sign, Gordon's sign); postural kinetic hand tremor; increased amplitude of leg tremor at rest (Fig. 2).

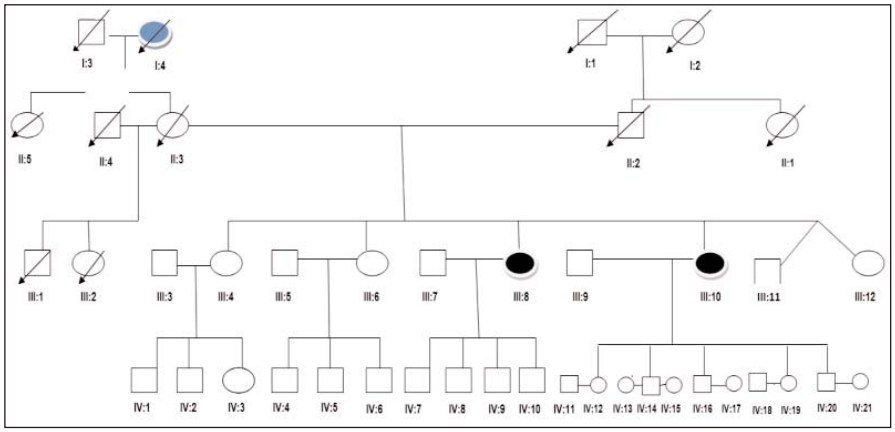

Figure 1. *The family pedigree chart of patients M. and G. I:4 – maternal grandmother supposedly had a neurodegenerative disease; III:8 – patient M. with parkinsonism and amyotrophic lateral sclerosis (ALS); III:10 – patient G. with Parkinson's disease.*

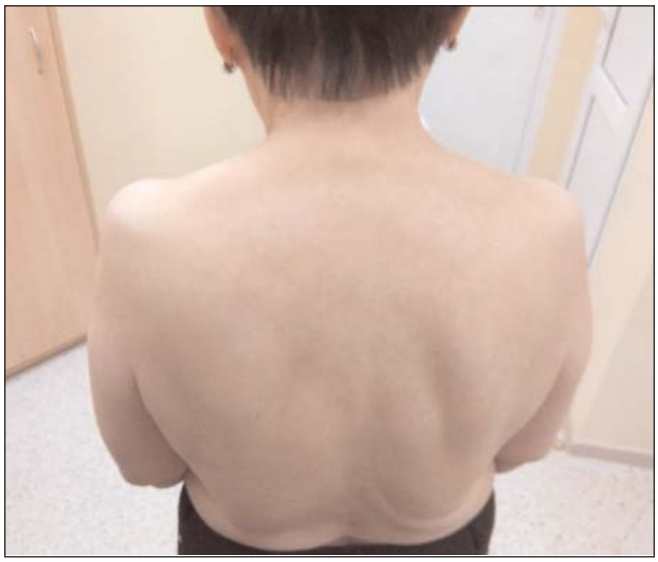

Figure 2. *Patient M., 62 years old.*

In cognitive status assessment, moderate cognitive disorders of dysregulatory type were noted. Electroneuromyography showed no pathology of peripheral nerves. Needle electromyography (EMG) demonstrated signs of denervation and reinnervation at the lumbar and sacral levels indicating the involvement of peripheral motor neurons in the pathological process (Fig.3 a–b).

Transcranial magnetic stimulation revealed signs of central motor neuron involvement which was manifested as an increase in the threshold of motor response and a decrease in its amplitude (Fig.4).

Magnetic resonance imaging (MRI) of the brain with a targeted study of the midbrain using susceptibility-weighted imaging (SWI) regimen, showed blurred boundaries of nigrosome 1, which was indicative of the involvement of the substantia nigra (Fig.5).

Thus, taking into account the progressive character of the disease, presence of parkinsonism with a positive response to dopaminergic therapy, signs of the involvement of both central and peripheral motor neurons, and absence of other clinically relevant neurological symptoms and dementia, the diagnosis of neurodegenerative disease with signs of parkinsonism, ALS and moderate cognitive impairment of dysregulatory type was made.

Case report 2. ***Patient G.***, *61 years old, a younger sister of patient M., was first admitted to the neurological department in 2016 with complaints of marked stiffness of arms and legs, slow movements, tremor of the left hand at rest and shuffling. She became ill in 2011 when she first noticed stiffness of her left extremities, which after 2 years spread to the right side; later, tremor of the left arm appeared. She was diagnosed with Parkinson's disease, and prescribed levodopa/ carbidopa at a dose of 750/ 75 mg/ day. After self-withdrawal of the medications, her symptoms became worse, muscle stiffness increased, and sometimes she became «frozen» when moving.*

Neurological examination revealed hypomimia, bradylalia, noticeable oligobradykinesia (more pronounced on the left), wide-amplitude tremor of the left hand at rest («pill rolling» type of tremor), diffuse muscle rigidity («lead-pipe» rigidity, more pronounced on the left), shuffling gait. Muscle hypotrophy, signs of pyramidal tract involvement, and fasciculations were not observed.

MRI with SWI regimen showed signs of substantia nigra involvement with blurred boundaries of nigrosome 1 zone.

The results of transcranial magnetic stimulation and needle EMG were normal.

After administration of levodopa/ carbidopa and pramipexole with dose titration, muscle rigidity and tremor decreased, the gait improved.

Taking into account typical clinical presentation and progressive character of the disease, the diagnosis was made: Parkinson's disease, mixed form, with predominant affection of the left extremities, stage III (the Hoehn and Yahr scale), moderate type of progressing.

Discussion. In 1973 K. Brait, S. Fahn and G. Schwarz [2] first described patients with symptoms of ALS on the background of parkinsonism. In one case the authors observed a rapid progression of the disease which two years later resulted in the patient's death; in the other cases the disease was less aggressive, and positive effect was achieved with levodopa treatment. In 2015 A.M. Erol et al.[3] published a detailed description of a patient with

Brait- Fahn-Schwarz disease whose condition also improved after therapy with levodopa; they presented the results of paraclinical investigations. Thus, EMG revealed signs of motor neurons involvement; magnetic resonance

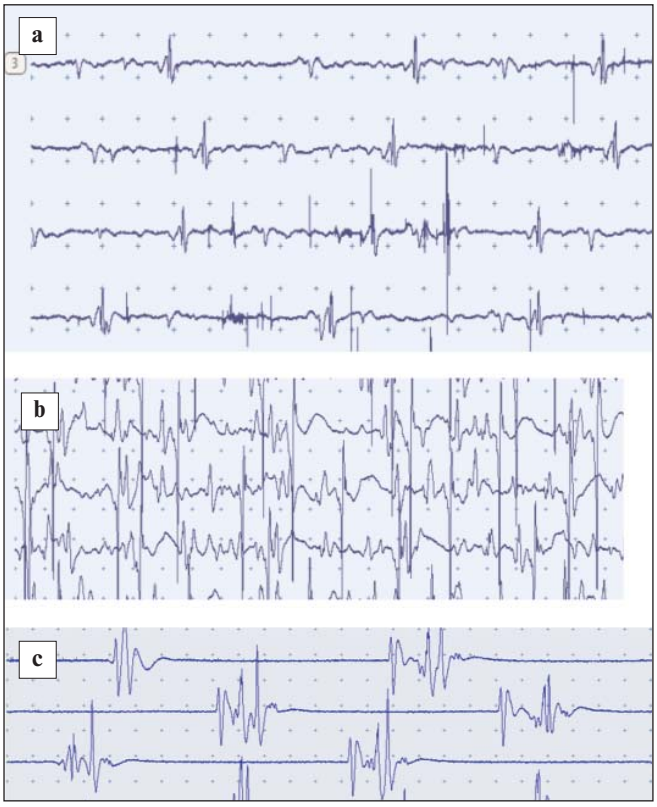

Figure 3. *Spontaneous activity in the studied muscles. a – m. deltoideus [right]: multiple potentials of fibrillations; b – m. extensor digitorum [right]: multiple potentials of fasciculations, fibrillations; c – m. tibialis anterior [left]: multiple potentials of fasciculations.*

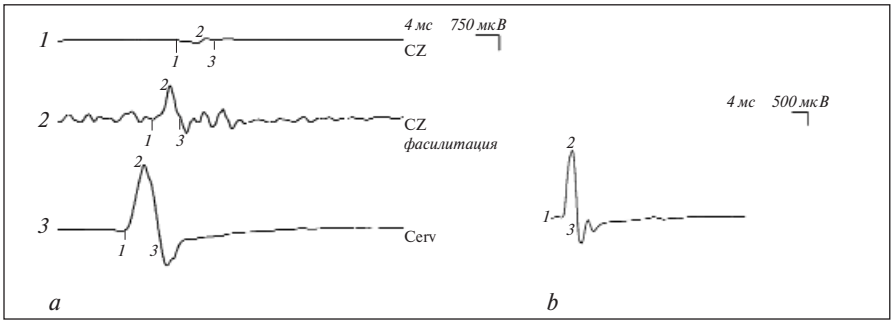

Figure 4. *Results of transcranial magnetic stimulation, target – m.abductor pollicis brevis [right]: a – cortical induced motor response (IMR) registered in the relaxed muscle (1); IMR in fascilitation of the target muscle (2); segmentary IMR at the cervical level registered in the relaxed muscle (3). Of note: IMR is significantly decreased in the relaxed muscle (0.076 mV) and reactivated in fascilitation (3.38 mV).The central motor conduction time (CMCT) is increased up to 9.18 ms (normal –7.7±1.1 ms); radicular delay is within the normal range – 0.8 ms. Amplitude ratio (IMR amplitude/ M-response amplitude) is significantly decreased – 2.9% (normal 25%–50%): b – results of registration of M-response from m. abductor pollicis brevis [right] at the level of the carpal canal; amplitude of M-response – 2.6 mV (normal – 3.5 mV), residual latency – 2.8 ms*

spectroscopy showed elevated levels of N-acetylaspartate and choline which are characteristic of degeneration of the pyramidal tract. The authors also carried out genetic analyses (genes *SOD1*, C9orf72 and *UBQLN2*), the results of which were negative.

Can Brait- Fahn-Schwarz disease be regarded as a separate nosological form from up-to-date standpoint? Undoubtedly, it belongs to a group of neurodegenerative diseases with uncertain etiology and pathogenesis. Extremely rare cases and absence of morphological data do not allow to regard it as an separate nosological entity. However, the term «Brait- Fahn-Schwarz disease» is used in international clinical practice, and can be considered acceptable, since the descriptions of the disease in different publications present a distinct clinical picture. Besides, these patients have a levodopa-responsive variant of the disease, which makes it different from ALS with extrapyramidal symptoms. This viewpoint is shared by A.M. Erol (3), C. Manno et al.(4) who suggest that a complex of Parkinson's disease and ALS is a separate nosological entity, and should be distinguished from extrapyramidal signs and symptoms typical of ALS.

In 1996 and in 2006 on Kii Peninsula, Japanese scientists examined 37 patients with symptoms of ALS in combination with parkinsonism and dementia. They divided the patients into 5 groups based on the clinical signs: 1) classical ALS; 2) ALS with dementia; 3) parkinsonism - dementia complex with predominant parkinsonism symptoms; 4) parkinsonism - dementia complex with predominance of dementia; 5) parkinsonism - dementia complex with symptoms of ALS. Thus, in this study there were no patients with ALS-parkinsonism without dementia (5). These data may also point out to Brait- Fahn-Schwarz disease as a separate nosological form with its own pathogenetic mechanisms which do not lead to dementia.

The probability of combination of Parkinson's disease and ALS as separate neurodegenerative diseases in patient M. is doubtful, because she and her younger sister had a similar picture of levodopa-responsive parkinsonism; besides, patient M. had moderate symptoms of ALS without a marked progressive course. In literature there are descriptions of cases of different neurodegenerative diseases in one family (6). But in our case, the prevalence of parkinsonism symptoms over the signs of motor neuron involvement in the elder sister reduces the possibility of comorbid conditions. Thus, we can suggest that both sisters have the same neurodegenerative disease despite the difference in clinical presentation. We cannot exclude the possibility that the younger sister will develop signs of motor neuron affection. In both cases we based our diagnoses on the criteria of the UK Parkinson's Disease Society Brain Bank (7) and El Escorial criteria for ALS (8). The hereditary character of the disease

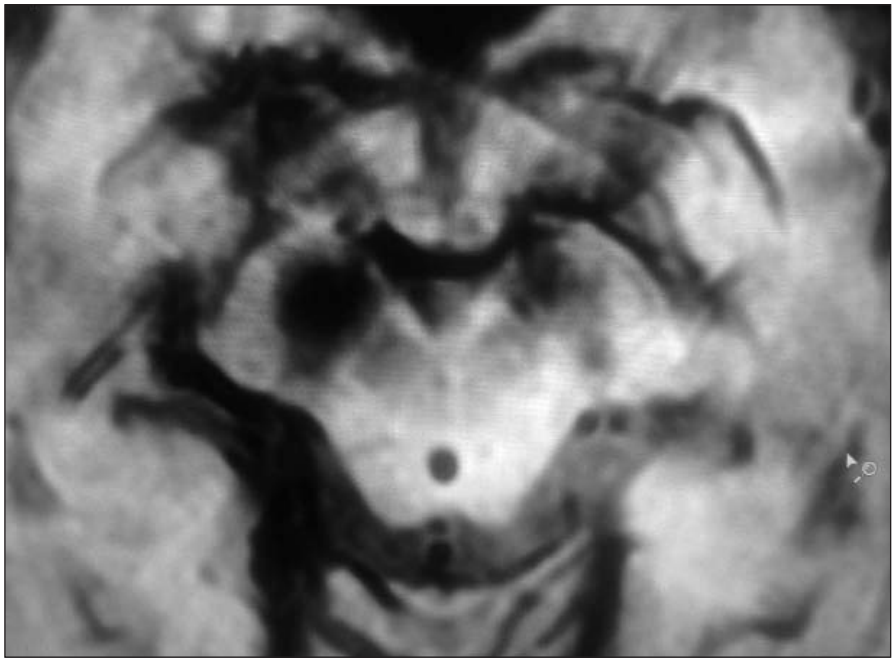

Figure 5. *Brain MRI with SWI regimen. Blurred boundaries of nigrosome 1 of the substantia nigra are seen*

is confirmed not only by blood relationship of the two patients, but by mentioning of the fact that their grandmother was suffering from a disease of legs and used a wheelchair. R.M. Wolf Gilbert et al. (9) among 7 cases of ALS-parkinsonism, described one family case as Brait-Fahn-Schwarz disease. The mean age of the patients in this group was 65 years. In our observation, the patients' age at the onset of the disease was 62 and 56 years old. S. Kuzuhara (10) suggested that the late onset of familial ALS with parkinsonism and dementia can be accounted for by the influence of some unknown environmental factors, modulating the process of genetically programmed disease, and difference in clinical presentation can be explained by phenotypically different manifestations (11). These suggestions may be applied to our clinical observation as well.

Can we regard the described familial case in the context of Guam type of ALS (ALS with the complex of parkinsonism and dementia) which was endemic in some locations of the Eastern-Pacific region (the Mariana Islands, Kii Peninsula, New Guinea) in the early 1960-s? Most cases of ALS with the complex of parkinsonism – dementia occurred in the west of New Guinea where the incidence was particularly high: 147 cases per 100 000 people. In the following 40 years there was a 5–10-fold decrease in the incidence of ALS in that region (12). C.C.Plato et al. (13) who had been studying this disease on the island of Guam for 60 years (until 1999), believed that a sharp decrease of the incidence was connected not with genetic factors but rather with a rapid westernization of Guam. However, it should be noted, that among the described cases from that region there were no patients with ALS with parkinsonism but without dementia. Given the local distribution of the disease and its sharp decrease in the endemic foci, we cannot exclude the influence of environmental factors which could cause a high incidence of the disease with similar symptoms in the area where both women live. However, there have been no such cases in this region. The absence of Guam type ALS without dementia in the endemic foci does not allow to regard this neurodegenerative disease as Guam type of ALS, but we do not exclude development of dementia in our patients in the future, or development of ALS in the younger sister.

Conclusion. Due to some differences in clinical picture in two siblings, we cannot state that the described case can be defined as Brait- Fahn-Schwarz disease, but similarity of the main symptoms and development of parkinsonism and ALS in one family point out to common mechanisms of the pathological process. The next step in our research will be genetic analysis (the whole-genome sequencing) to identify possible causative mutations.

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