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A TYPICAL FORMS OF ALS: REVIEW AND OBSERVATION FROM PRACTICE

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Abstract: The combination of parkinsonism with other neurological disorders, such as autonomic failure, dementia, cerebellar ataxia, visual disturbances, pyramidal syndrome, is characteristic of some neurodegenerative diseases, for example, multisystem atrophy, dementia with Lewy bodies, progressive supranuclear palsy, corticobasal degeneration. These diseases are often found in the practice of a neurologist, have a detailed description and clear diagnostic criteria.

The isolated combination of parkinsonism and ALS (without other neurological disorders) is extremely rare and is called Bright-Fan-Schwarz disease in honor of the scientists who first reported this cross-syndrome.

We did not find descriptions of cases of familial neurodegenerative disease with parkinsonism and ALS in the literature. This article presents the authors' own observation of three siblings, one of which had parkinsonism with ALS syndrome, and the other two had Parkinson's disease.

The combination of amyotrophic lateral sclerosis (ALS) with Parkinson's syndrome and dementia is described as Guam-type ALS, in which up to 70% of patients have a positive family history.

Keywords: parkinsonism; Parkinson's disease; Guam-type amyotrophic lateral sclerosis; electromyography; transcranial magnetic stimulation; Bright-Fan-Schwartz disease.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease accompanied termination of central and peripheral motor neurons , steady progression and death. Recently, there has been a trend towards an increase in the incidence of ALS in all age groups, and primarily among people of mature and working age with high professional and intellectual potential.

Currently, it is believed that ALS is a multifactorial and multisystemic disease that is associated with a genetic predisposition and is provoked by environmental factors [7]. It has been shown that many interacting factors are involved in the pathogenesis of ALS. These are genetic factors, oxidative stress, glutamate excitotoxicity, damage to such important intracellular organelles as mitochondria, protein aggregates, damage to the cytoskeleton and components of the axonal transport system. These mechanisms do not necessarily act on their own, they are interrelated and lead to disruption of calcium homeostasis, which is the central link. Recently, increased attention has been paid to the role of glial cells [3], which normally surround motoneurons in the CNS, as well as the

role of impaired response to hypoxia in the pathogenesis of MND. Undoubtedly, important information about the pathogenesis of MND has been obtained from studies of genetic subtypes of MND, especially those associated with mutations in the SOD-1 gene. The infectious and autoimmune hypotheses of the origin of MND are not considered at the moment. The search for a possible cause of the death of motor neurons and the construction of hypotheses for the pathogenesis of this disease continue.

Currently, the selectivity of motor neuron damage in ALS is questioned. There are studies confirming the multisystem nature of MND: this disease affects not only motor neurons, but also other brain structures [3], and skin [7]. The fact of the combination of ALS with dementia disorders is very interesting. In typical cases of ALS, clinically dementia is not observed. But, according to different researchers, in 5-20% of ALS cases it is combined with frontotemporal dementia (FTD) [4]. In turn, FTD in 10% is accompanied by the development of a clinic of generalized damage to motor neurons [2].

FTD is a disease characterized by progressive degeneration of neurons in the frontal and anterior temporal lobes, clinically manifested by early behavioral disorders, impoverishment of speech up to aphasia, with almost intact memory. For the first time, the relationship between ALS and FTD was noted at the end of the 19th century, and subsequently, many researchers described violations of frontal functions in both familial and sporadic cases of ALS [4,5]. At the same time, it was noted that dementia can either precede the development of the ALS clinic or be observed later. Chromosome loci responsible for the development of a special form of neurodegeneration combining ALS and FTD have recently been identified [1].

Modern diagnostics is complicated by the presence of atypical forms, combination with various neurological nosologies and syndromes. One of the options for the atypical course of amyotrophic lateral sclerosis is a combination with parkinsonism and dementia (Guam's disease), an endemic form. The form of the disease with parkinsonism without cognitive impairment is now increasingly common. Parkinsonism can be both levodopa sensitive and resistant to treatment. In recent years, cases of isolated combination of ALS with levodopa-sensitive parkinsonism have been reported, which is called Bright-Fan-Schwarz disease.

The aim of this study was to evaluate the cognitive functions of patients with ALS. We examined 20 patients (11 men and 9 women) with reliable and probable ALS (according to the El Escorial diagnostic criteria, 1998). The age of the patients ranged from 38 to 67 years, the average age was 51.25ё1.75 years. The duration of the disease varied from 6 months to 2 years. Two patients suffered from arterial hypertension, none had a history of cerebrovascular pathology (including ischemic stroke), diabetes mellitus, none of the patients was taking psychotropic drugs. The control group consisted of 13 volunteers (6 men and 7 women) with no history of neurological or psychiatric diseases, the average age in the group was 48.36ё1.84 years. To assess the neuropsychological status, the following methods were used: a brief mental status assessment scale (MSSS) to rule out clinically obvious dementia, a battery of frontal tests (conceptualization, dynamic praxis, simple choice reaction, complicated choice reaction, examination of grasping reflexes) [1], test of verbal associations (literal and categorical) to assess fluency, test of 5 words to assess memory function. Patients with speech disorders (bulbar, pseudobulbar syndromes) were not excluded from the study, because when assessing fluency, a written version of the verbal associations test was also performed. Statistical processing was carried out on a computer using the statistical package Statgraph. The reliability of differences in mean indicators between groups was assessed by Student's criterion, non-parametric indicators - by criterion2. Differences were considered significant at p0.05.

Of the 20 examined patients with ALS, 1 patient was diagnosed with dementia and parkinsonism, which, in accordance with the diagnostic criteria of Neary (1998), could be regarded as frontotemporal dementia or Bright-Fan-Schwarz disease. The diagnosis of ALS in this patient was reliable. During dynamic observation for 1.5 years, it was noted that both types of neurodegenerative disorders, combined in one patient, developed in parallel, but the severity of the condition in the initial stages of the disease was due to changes in the cognitive sphere. This observation allowed us to settle on the diagnosis of ALS-dementia. In the rest of the patients, according to the (MSSS) and the battery of frontal tests, cognitive changes did not reach the level of dementia.

When performing tests of literal and categorical verbal associations (oral and written), a significant decrease in the number of called/written words was revealed compared to the control group. Also, in the main group, a significant decrease in the total score was revealed according to the results of the battery of frontal tests. At the same time, when statistically processing the data obtained during the test of 5 words, a statistically significant difference between the groups was not established.

Our study confirmed the assumption that ALS patients without clinically defined dementia have a selective impairment of cognitive functions, in particular, speech fluency suffers. Obviously, ALS patients require a more in-depth neuropsychological examination. Such severe symptoms as pronounced motor disorders, dysphagia, dysarthria mask and make the patient's cognitive deficit or even dementia disorders less significant. However, the mere presence of changes in neuropsychological status requires additional recommendations for carers and, in some cases, correction of therapy.

As noted by many researchers, the profile of changes in the neuropsychological status of patients with ALS is similar to that in PTD, which also indicates the relationship of these degenerative diseases [1, 4]. Until now, it remains unclear whether cognitive impairment in ALS is an early stage of the pathological ALS-dementia complex, or whether such a complex is a separate nosological form. But the frequent combination of these conditions suggests a commonality of their etiology, which opens up new opportunities for research at the clinical, morphological, genetic levels and the search for new ways of therapy.

Extremely rare cases and the lack of morphological data do not allow us to regard it as an independent form. But in international clinical practice, the term "Bright-Fan-Schwartz disease" is used, which can be considered acceptable, since the descriptions of this disease presented in the literature have a characteristic clinical picture. In addition, these patients had a levodopa-responsive variant of the disease, which distinguishes it from ALS-plus with extrapyramidal symptoms. The same opinion is shared by A.M. Erol [3] and C. Manno et al. [4], who suggested that the complex of Parkinson's disease and ALS is an independent nosology that should be separated from extrapyramidal signs and symptoms characteristic of ALS. In 1996 and 2006 On the Kii Peninsula, Japanese scientists examined 37 patients with ALS in combination with a complex of parkinsonism - dementia. At the same time, they divided the patients according to clinical signs into five groups: 1) classic ALS; 2) ALS with dementia; 3) complex parkinsonism - dementia with a predominance of symptoms of parkinsonism; 4) complex parkinsonism - dementia with a predominance of dementia; 5) complex parkinsonism - dementia with symptoms of ALS. As can be seen, there were no patients with ALS-parkinsonism without dementia in this study [5]. These studies may also point to Bright-Fan-Schwarz disease as an independent disease with slightly different mechanisms of pathogenesis that do not lead to the development of dementia.

The possibility of a combination of Parkinson's disease and ALS in patient M. as two independent neurodegenerative diseases seems doubtful, since both she and her younger

sister had a typical picture of levodopa-responsive parkinsonism, and patient M. had moderate clinical symptoms of ALS without a pronounced progredient currents. The literature describes cases of various neurodegenerative diseases in the same family [6]. But in the case presented by us in the older sister, the prevalence of symptoms of parkinsonism over signs of motor neuronal damage reduces the likelihood of a comorbid condition. This suggests that the sisters suffer from the same neurodegenerative disease, despite the difference in clinical presentation. Perhaps in the future, the younger sister will develop signs of damage to motor neurons. When diagnosing in both cases, we took into account the criteria of the Brain Bank of the Parkinson's Disease Society of Great Britain [7] and the El Escorial criteria for ALS reliability [5]. In favor of the hereditary factor in the case described by us, in addition to the consanguinity of women, the mention of the grandmother, who suffered from a leg disease and moved in a wheelchair, also testifies. RM Wolf Gilbert et al. [7] described one familial case as Bright-Fan-Schwartz disease among 7 recorded cases of ALS parkinsonism. The mean age of patients in this group was 65 years. In our observation, the age of onset of the disease was 62 and 56 years. S. Kuzuhara suggested that the late onset of hereditary ALS with a parkinsonism-dementia complex can be explained by the influence of some unknown environmental factors that modulate the process of a genetically programmed disease, and the difference in the clinical picture can be explained by phenotypically different manifestations [1]. Perhaps these assumptions are applicable to our clinical observation. Can we consider the familial case described by us within the framework of the Guam-type ALS (ALS with parkinsonism-dementia complex), found in endemic foci of the Eastern Pacific region in the early 1960s? (Marian Islands , Kii Peninsula, New Guinea).

Most cases of ALS with parkinsonism-dementia complex were observed in the west of New Guinea, where the incidence was especially high and amounted to 147 cases per 100,000 population. In the next 40 years, the incidence of ALS in the East Pacific region decreased by 5-10 times [2]. S.S. Plato et al. [13], who studied this disease on the island of Guam for 60 years (until 1999), believed that the sharp decrease in the incidence was not due to genetic factors, but rather to the rapid westernization of Guam. It should be noted that among the sick and in other endemic foci of the East Pacific region, there were no cases of ALS with parkinsonism syndrome without dementia . Given the locality of the disease with its sharp decline in endemic foci, it is still impossible to exclude the influence of environmental factors that should have caused a high incidence with similar symptoms in the region of residence of both women. No such cases have been found in this region. The absence of cases of Guam-type ALS without dementia in endemic foci also does not allow us to classify this neurodegenerative disease as Guam-type ALS. However, we do not rule out the possibility of developing dementia in our patients in the future, as well as the appearance of ALS syndrome in a younger sister.

Conclusion. Thus, due to some differences in the clinical picture in siblings, we cannot assert that the family case described by us can be attributed to Bright-Fan-Schwarz disease, but the similarity of the main symptoms and the development of parkinsonism and ALS within the same family indicate the unity of the pathological mechanisms. process. The next stage of our research will be a genetic study (whole genome sequencing) to identify possible causative mutations.

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