Successful Treatment of a Patient with Lhermitte-Duclos Disease (a Case Report and Literature Review)

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**Background.** Lhermitte-Duclos disease is a rare autosomal dominant inherited disease characterized by the loss of the normal cerebellar cortex architecture and the formation of cerebellar hamartoma. The disease usually manifests in the 3rd—4th decade of life. To date, approximately 220 cases of Lhermitte-Duclos disease have been reported in the medical literature. Result. Successful two-stage surgical treatment of a young female patient with Lhermitte-Duclos disease was performed. **Conclusion.** This rare case introduces the clinical presentations and radiographic features of the disease to practitioners, which may facilitate timely diagnosis and proper treatment of the condition.

**Keywords:** Lhermitte-Duclos disease, dysplastic gangliocytoma, inherited disease, PTEN gene, neurosurgical treatment.

Lhermitte-Duclos disease, also known as dysplastic cerebellar gangliocytoma, was first diagnosed by doctors Lhermitte and Duclos in 1920. In subsequent years, the disease was described by many researchers: Bielschowsky and Simons in 1930, Christensen in 1937, Duncan and Snodgrass in 1943, Ambler in 1969, and Padberg in 1991. Each of the authors referred to this disease in a different way: diffuse gangliocytoma of the cerebellum, purkinjeoma, hamartoma, dysplastic gangliocytoma, diffuse ganglieneuroma, and granule cell hypertrophy of the cerebellum. In total, about 220 cases of Lhermitte-Duclos disease have been described in the literature [1].

In 1920, Lhermitte and Duclos described a disease in a 36-year-old male who first developed symptoms of hearing loss on the left and occipital pains at the age of 10 months. Before admission, the patient had paroxysmal vertigo with repeated falls. Examination revealed cerebellar ataxia, dysarthria, nystagmus, and neuropsychic disorders with disorientation and memory impairment. One week after admission, the patient’s condition deteriorated. He was not operated on; the patient’s consciousness level gradually decreased to a coma, and he died.

Considering the disease nature, Lhermitte and Duclos suggested that a pathological lesion found in the posterior cranial fossa during autopsy was a combination of a congenital malformation and a tumor developed from ganglion cells [1, 2].

In 1937, Christensen reported the first successful surgery for dysplastic gangliocytoma of the right cerebellar hemisphere. The surgery was carried out in a 34-year-old male who had suffered the disease since the age of 6 years. The patient had rises in blood pressure, occipital and temporal headaches, nausea, and vomiting at the peak of headache. Sometimes these attacks resulted in the loss of consciousness. The findings at admission included bilateral papilledema, trigeminal nerve impairment on the left, and the right facial paralysis. Ventriculography revealed a displacement of the fourth ventricle and aqueduct to the left. During surgery, a viscous, poorly demarcated, glioma-like mass was found in the right cerebellar hemisphere. The mass was removed, and the patient was discharged without complaints. The patient returned to his work 18 months after surgery. The subsequent course of the disease was not monitored [3].

Now, Lhermitte-Duclos disease is proved to be a hamartoma rather than a tumor [4]. A differential diagnosis of hamartomas and neoplasms is based on preservation of laminated structures of the cerebellum in congenital malformations. Cyst formations, which are usually associated with tumors, are not typical of Lhermitte-Duclos disease. The disease is inherited in an autosomal dominant manner and is caused by a mutation of the phosphatase and tensin homolog (PTEN) gene in chromosome 10q23.31. Approximately 90% of patients with dysplastic cerebellar gangliocytoma have a mutation in this gene or its promoters. The PTEN gene was first identified as a tumor suppressor in glioma. Researchers associated somatic mutations of the gene with glioblastoma, melanoma, and endometrial and prostate cancers. The gene encodes lipid phosphatase for phosphatidylinositol-3-kinase, inhibits serine/threonine kinase formation, alters the phosphatidylinositol 3-kinase pathway, and thereby enhances apoptosis [5—7]. However, despite a large number of studies, the exact etiology and pathogenesis of Lhermitte-Duclos disease still remain unknown [8, 9].

The disease can be diagnosed at an early age when the first clinical signs of the degenerative pathology in the posterior cranial fossa develop. The duration of symptom manifestation varies from a few months to many years. The largest accumulation of abnormal cells in dysplastic cerebellar gangliocytoma is usually formed by the 3rd—4th decade of life, which is featured in the time course of clinical symptoms [10]. Impairment of the cranial nerves,
Fig. 1. T2-weighted MRI.
Hyperplasia of the right cerebellar hemisphere. Obstructive hydrocephalus.

Fig. 2. SCT angiography.
A dilated occipital vein is seen, which was erroneously identified as an arteriovenous malformation.

Fig. 3. Right-sided cerebral angiography.
Lateral (a) and frontal (b) views. A displacement superiorly and medially to the initial segment of the right posterior cerebral artery and a displacement of the right posterior inferior cerebellar artery behind the midline are observed. Its caudal loop descended into the spinal canal. Wide spreading of the hemispheric branches of the right superior cerebellar arteries is seen.

Fig. 4. Axial view of the brain MRI (T2-weighted mode) demonstrates a patchy pattern of the right cerebellar hemisphere and an increased size of the cerebellum.
IV ventricle is shifted to the left and narrowed. III and lateral ventricles are dilated.
cerebellar ataxia, and clinical manifestations of intracranial hypertension are most often caused by acute or chronic hydrocephalus.

In practice, there are cases of the asymptomatic disease course. In 1969, Ambler described the first familial case of dysplastic cerebellar gangliocytoma observed in a 32-year-old male who died from the disease. Death of his mother was not associated with Lhermitte-Duclos disease. However, conducted investigation revealed that she was a carrier of the asymptomatic disease, which manifested in macrocephaly only. Some members of her family also had a large head circumference; all of them, as emphasized by the author, were asymptomatic carriers of the tumor. Macrocephaly, as one of the additional abnormalities associated with Lhermitte-Duclos disease, occurs in about 50% of cases [2].

Some authors have described this disease in the association with Cowden disease, also known as multiple hamartoma syndrome. Cowden disease is a rare autosomal dominant familial syndrome with a high degree of penetrance and a significant risk for developing breast cancer. Clinically, the disease is characterized by multiple hamartomas. Breast cancer develops in about 30—50% of cases, and thyroid cancer develops in 10% of cases. In 1996, Nelen discovered the Cowden disease gene in chromosome 10q22-23, which partially overlaps with the PTEN locus. This strong tumor suppressor gene was named PTEN/MMAC1. Currently, tumor lesions associated with Cowden disease are proved to occur mainly due to vertical transmission of mutations of this gene [11, 12].

Malformations and a number of other disorders are associated with Lhermitte-Duclos disease to varying degrees. For example, macrocephaly, hydrocephalus, syringomyelia, and skeletal abnormalities (polydactyly, syndactyly, asymmetry of the facial bones) often occur. Lesions, such as lipomas, neurofibromas, hemangiomas, and tongue papules, are less common. Sometimes, Lhermitte-Duclos disease is accompanied by lesions of the...
thyroid gland, breast, genitourinary system as well as by gastrointestinal disorders.

The main methods of instrumental diagnostics of Lhermitte-Duclos disease include magnetic resonance imaging (MRI) and computed tomography (CT) of the brain [13—17].

Here, we present a clinical case of the disease and its treatment.

A 17-year-old female patient S. was admitted to the Neurological Institute. A few months before admission, she began to note a shaky walk and periodic headache. The neurological status revealed occlusive, cerebral, and pronounced cerebellar symptoms. According to a past medical history, the patient underwent strumectomy for thyroid tumor in 2002 and received L-thyroxine. Since 2006, she was followed-up for macrocephaly.

MRI of the brain revealed a space-occupying mass of the right cerebellar hemisphere and obstructive hydrocephalus with periventricular edema signs (Fig. 1). On the basis of CT performed in a vascular regimen, an arteriovenous malformation of the right cerebellar hemisphere was suggested (Fig. 2). To clarify the diagnosis, cerebral angiography was performed that did not confirm the arteriovenous malformation diagnosis (Fig. 3).

Repeated MRI, which the patient underwent at the Neurosurgical Institute, confirmed the previously identified pathology (Fig. 4).

Retrospective analysis of the scans, which had been taken for macrocephaly in 2006, revealed a small space-occupying mass in the right cerebellar hemisphere, which was almost identical to the substance of the cerebellum (Fig. 5).

Thus, it may be concluded that significant growth of the gangliocytoma occurred in the puberty period. The patient underwent ventriculoperitoneal shunting for clinical and radiographic signs of obstructive hydrocephalus with periventricular edema. After resolution of hydrocephalus, the patient retained prolapse of the cerebellar tonsils into the foramen magnum (Fig. 6, 7), which re-
quired decompression of the craniovertebral junction and a biopsy of the cerebellar lesion (Fig. 8).

Later, we conducted genetic and morphological analysis that confirmed a mutation of the PTEN gene in chromosome 10q23.31. This verified the diagnosis of Lhermitte-Duclos disease and excluded other syndromes.

Microscopic examination of a gangliocytoma reveals a drastic expansion of the internal granular layer of the cerebellum, which contains a plenty of large neurons with vesicular nuclei. These neurons significantly exceed the size of normal cells, but they are a little bit lesser than Purkinje cells. Neurons of gangliocytoma do not divide, but the tumor size can slowly increase due to growth and myelination of neuronal processes (Fig. 9) [5, 18, 19].

During follow-up, the patient had complete regression of cerebellar ataxia and cerebral symptoms. At the time of writing this paper, the patient was followed up by an endocrinologist, geneticist, gynecologist, and a therapist due to a risk of injury to the breast and genitourinary system. The total follow-up period amounted to 5 years. During this period, no gangliocytoma growth was observed. The patient was socially integrated.


REFERENCES


Conclusions

Lhermitte-Duclos disease is a rare disease with slow aggravation of symptoms. It manifests mainly in the puberty period or 3rd—4th decade of life. The age range may vary from early childhood to extreme old age. Identification of clinical symptoms and genetic analysis at the early stages of the disease enable timely surgical intervention to increase the quality and length of life of the patient.

The choice of surgical intervention requires a detailed analysis of the clinical and neuroradiological data. The lack of a distinct boundary between a pathological lesion and a healthy cerebellar tissue constitutes a great technical problem for resecting hamartoma. This aspect is confirmed by histopathological examinations that reveal the lack of a transitional area between normal and abnormal cortical tissue [7]. Unlike the normal cerebellar tissue, the pathological lesion has a pale color and is usually located in deep-seated portions of the cerebellum, not on its surface [20, 21]. In this regard, radical surgery is not the best choice because it is associated with a high risk of disability in the patient.
The article presents a case of successful treatment of a rare genetically determined disease of the cerebellum — Lhermitte-Duclos disease. Despite the fact that the disease was first diagnosed in 1920, about 220 cases of the disease (which is probably a dysgenetic malformation of cerebellar neurons) have been reported in the literature so far. The described case demonstrates the completeness of patient examination using a number of modern neuroradiological techniques as well as genetic analysis, which revealed a constitutional mutation of the PTEN gene, typical of this pathology.

The authors performed staged surgical treatment of the pathology using modern technologies (e.g., neuronavigation). The first stage was ventriculoperitoneal shunting to resolve hydrocephalus, and the second stage included decompression of the craniovertebral junction with autograft plasty of the dura mater and a neoplasm biopsy. The postoperative follow-up period was 5 years. Regression of occlusive, cerebellar, and cerebral symptoms was observed in the patient. No continued growth of the gangliocytoma within the follow-up period was detected. The patient was socially integrated and able to work, which is an important factor because the disease usually occurs during the puberty period or 3rd—4th decade of life. The presented paper will be useful to a wide range of specialists: neurosurgeons, neurologists, endocrinologists, therapists, and urologists.

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