NEUROFIBROMATOSIS TYPE II: A CASE REPORT

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S u m m a r y. Neurofibromatosis (NF) is a heterogeneous group of neurocutaneous diseases, which is generally characterized by an increased predisposition to various types of tumors of the nervous system. Neurofibromatosis type 2 (NF2) is generally less frequent than neurofibromatosis type 1 (NF1) and affects 1 in 25,000 births (approximately 10% of all patients with NF). It is caused by mutations in the *NF2* gene at the locus of 22q12. *NF2* is manifested by tumors in the central nervous system (CNS), especially by bilateral vestibular schwannomas, also known as acoustic neuromas (that often lead to hearing loss) and numerous meningiomas. While NF1 affects mostly the skin, peripheral nerves, eyes, and less frequently bones and internal organs, NF2 is characterized by a much worse prognosis affecting mostly CNS. In the study we report a case of a 21-year-old patient with NF2 and bilateral acoustic neuromas. The disease caused a significant degree of disability in the patient. At such a young age, he suffers from blindness, significant loss of hearing and is largely dependent on other people when it comes to daily functioning.
K e y w o r d s: neurofibromatosis, bilateral vestibular schwannomas, epilepsy.

INTRODUCTION

Neurofibromatosis is a heterogeneous group of neurocutaneous diseases, which is generally characterized by an increased predisposition to various types of tumors of the nervous system. The first clinical case description is attributed to Italian doctor Ulisse Aldrovandi, who described a man of short stature with a large tumor resembling an isolated plexiform neurofibroma in 1592 [1]. Neurofibromatosis type 1 (NF1) is characterized mainly by the presence of neurofibromas and fibromas, pedunculated tumors can occupy the entire body. Moreover, gliomas often occur, too [2]. On the other hand, bilateral (or unilateral less frequently) tumors in the Schwann cells of the vestibular nerve are characteristic of neurofibromatosis type 2 (NF2). Other cranial nerves may also be involved in NF2, in addition, meningiomas are often present, especially in the anterior fossa of the skull. Neurofibromas are relatively rare, and very few in number [3, 4]. In both types, but primarily in the course of NF1, the presence of skin lesions is characteristic, the most typical of which are 'café-au-lait' spots [5, 6]. The genetic alterations are detected on chromosome 17-17q11.2 in NF1, and chromosome 22-22q12.2 in NF2 [7, 8, 9].

MATERIALS, METHODS AND AIM

The present article reviews research reports on neurofibromatosis with special focus on NF1 and NF2. In the study we report a case of a 21-year-old male patient with NF2 who was admitted to the Department of Neurology.

CASE REPORT

A 21-year-old male patient who was diagnosed with NF2 in childhood was admitted to the Department of Neurology after the first fit of epileptic seizures. The cause of the disease is a mutation in the gene located at 22q12.2 of chromosome 22. The patient underwent thoracic surgery (anterior mediastinal tumor surgery) seven years ago. In addition, he was operated on for the removal of fibrous meningioma of the anterior cranial fossa, that caused blindness four years earlier. The patient

began to develop progressive hearing loss (associated with vestibular tumors).

During hospitalization in the Department of Neurology, neurological examination revealed: anisocoria (L>R), binocular blindness, bilateral hearing loss, asymmetry of the face (lower setting of the right angle of the mouth), Babinski sign was absent. Patient's gait was uncertain and required the help of another person. No symptoms of meningitis were observed. A series of additional tests were performed. The MRI scans were compared with those taken in 2017. The MRI scans of the head of 2017 revealed the dilatation and inclination towards postoperative changes of the right frontal corner. They also showed two areas of contrast enhancement in the left ventricle lateral occipital triangle, probably meningiomas. The current MRI scans of the head showed a significant dimensional progression of vestibular schwannomas, exerting marked pressure on the stem on the right side. In addition, the scans showed extensive postoperative changes at the base of the frontal lobes, and after intravenous administration of the contrast agent, a slight contrast enhancement of the frontal meninges was visible. The EEG record was abnormal, with changes in the frontal area on both sides the majority of which on the right side in the form of delta waves, the basic pattern was disorganized with single or grouped low-voltage slow theta waves, especially in the right parietal-occipital-posterior area. During the hospitalization symptomatic focal epilepsy was diagnosed and the patient was treated with an antiepileptic drug - Levetiracetam (2x750mg). Due to bilateral vestibular schwannomas pressing on the brainstem, which could lead to worsening of the symptoms, even death, the date of neurosurgical treatment was decided. The patient was waiting for surgical intervention at home. Three weeks later, the patient was readmitted to the Department of Neurology for the deterioration of contact, right-sided paresis, and an increase in epileptic seizure severity.

Neurological examination performed at that time revealed anisocoria, binocular blindness, bilateral hearing loss, asymmetry of the face and right-side paresis of limbs. To treat epileptic seizures 2x1000 mg of Levetiracetam was introduced to decrease the frequency of epileptic seizures. The patient was transferred to the Neurosurgery Clinic for surgery. The patient was consulted by a team of specialists who decided not to operate on him because of the high risk of complete hearing loss, and little possible benefits and outweighing potential damage that the surgery could have caused. The patient was therefore discharged with a referral to the Oncology Clinic.

DISCUSSION

Symptoms of NF2

NF2 is an inherited autosomal disease manifested by an increased tendency to develop tumors, in particular tumors of Schwann cells and meningiomas. Diagnosis usually follows two ways. It may be based on a genetic test, when a pathological mutation of the *NF2* gene is found [10]. The cause of the disease is a mutation in the gene located at 22q12.2 of chromosome 22 [7, 8]. In the absence of genetic testing, the disease can be diagnosed when certain clinical criteria are met.

The criteria for the diagnosis of NF2 have been elaborated by the National Institute of Health (NIH), and, generally speaking, allow to identify the disease in two situations. One of them is the most classic example of NF2, i.e. the occurrence of bilateral vestibular nerve tumors in the Schwann cells [8, 11]. The reported case describes bilateral vestibular schwannomas. The other situation assumes family history of *NF2*. Then, only unilateral vestibular nerve tumor of the Schwann cells is enough to diagnose the disease or, which is less typical, any two tumors such as meningiomas, gliomas, neurofibromas, tumors of the Schwann cells (other nerves than the vestibular nerve), or posterior sub-ocular opacification [8, 12, 13]. Vestibular tumors of the Schwann cells also called vestibular schwannomas or acoustic neuromas are the most typical of NF2, if occurring on both sides allow to diagnose the disease [14]. They mainly concern the eighth cranial nerve, i.e. the vestibulo-cochlear nerve appearing behind its embranchment in two parts, they occur in the upper part or the vestibular branch of this nerve. Symptoms are the result of nerve compression and destruction, especially the cochlear branch (which results in hearing loss and later even complete loss and tinnitus), and at the late stages also surrounded by the tumor (which is sometimes compared to the bunch of grapes) the vestibular branch (which in turn, results in disturbances in balance) [12]. As the vestibulo-cochlear nerve connects with the CNS at a place called the cerebello-pontine angle, on the border of the cerebellum and the brainstem, tumors in this location may produce a set of symptoms called the cerebello-pontine angle syndrome. It consists of

the already mentioned hearing disorders and dizziness, and the symptoms of pressure on the nearby nerves V and VII (disturbances in the facial sensation, facial expressions, Bell's paralysis), and less often the nerves IX, X and XII. In addition, there are symptoms of pressure on the cerebellum, medulla oblongata (pyramid symptoms on the opposite side) and the brainstem, where the damage to vital centers may pose a high risk of death for patients with NF2.

The prognosis in patients with NF2 is not very good. The disease shortens life expectancy, and it reduces the quality of life dramatically, which is a much more important problem for doctors and patients. Our young patient suffers from blindness and significant loss of hearing, and is largely dependent on other people when it comes to daily functioning. Before 1990, the survival rate did not exceed 15 years from the diagnosis, and although some progress has been made in earlier detection and in more effective treatment or even better disease control, many patients still die young [15].

Treatment of NF2

The treatment and care of patients with NF2 should involve regular assessment and monitoring of hearing loss, eye tests and MRI. Only early detection of tumors gives a chance for successful surgery. Surgery remains the preferred method of treating symptomatic tumors, radiation is another option. Surgical treatment of vestibular tumors of the Schwann cells in the course of NF2 is usually more difficult than in sporadic cases, mainly due to their multifocal nature (above mentioned comparison to grape bunches). Due to difficult surgical locations, there is a high risk, often the certainty of hearing loss during surgery. Also, despite numerous improvements in surgical methods in recent years, facial and trigeminal nerves in the area may get damaged. The decision to undertake or abandon surgery should be adjusted to individual patient [16]. It is necessary to look mainly through the prism of quality of life loss due to possible or often even impossible to eliminate complications, sometimes overweighing the potential benefits that treatment may bring [17]. Some of the tumors should be left for observation. In addition, it is recommended to take MRI scans, the head should be scanned once a year, and the spine once every four years. At such a young age, our patient suffers from blindness and significant loss of hearing. After a team decision, the surgery for the reported case was not decided due to the high risk of complete hearing loss and little potential benefits in comparison to the potential damage that the surgery could have caused.

Although, as already mentioned, the treatment is mainly surgical, research on various types of pharmacotherapy is ongoing. One of the medicines used is bevacizumab, a monoclonal antibody which is a vascular endothelial growth factor (VEGF) inhibitor [18, 19]. As reported by Sverak et al., bevacizumab treatment brought hearing improvement in 56% of patients, while decreased tumor volume was noted in 47% of cases [18]. Although only half of the patients experienced positive effects such as a reduction in tumor size or improvement or at least delayed hearing loss, it is undoubtedly a promising direction for neuroncology development. The use of bevacizumab probably improves the likelihood of hearing preservation in growing tumors in the short term [20, 21]. Bevacizumab is more effective than hearing sparing surgery and radiotherapy in preserving hearing in cases of NF2 [20]. The combination of bevacizumab with other molecular targeted drugs, such as lapatinib and erlotinib may generate synergistic effect but the efficacy of this treatment must be confirmed by clinical trials [22]. There are also other potential targets of modern NF2 therapies effective at various stages of the intercellular signaling pathways using neurofibromin 2 (merlin). However, groundbreaking reports are still to come.

CONCLUSIONS

NF2 is an autosomal dominant hereditary disease and a heritable tumor predisposition syndrome that leads to the development of multiple intracranial tumors, including meningiomas and schwannomas [13, 23]. Sporadic mutations represent 50% of NF2 cases [22]. While NF1 affects mostly the skin, peripheral nerves, eyes, and less frequently bones and internal organs, NF2 is characterized by a much worse prognosis affecting mostly the CNS. Vestibular schwannomas are the hallmark lesions, affecting 95% of patients with NF2 [8]. In the reported case, the disease caused a significant degree of disability in the patient. At such a young age, the patient suffers from blindness, significant loss of hearing, and is largely dependent on other people when it comes to daily functioning. Risk of early mortality from the brainstem compression and other complications is also important. Severity of disease is higher when NF2 is diagnosed in childhood. The decision of surgery depends on possible

benefits in comparison to the potential damage that the surgery could cause. The prognosis in patients with NF2 is not very good and symptoms may occur with varying severity. International collaboration could find ways to slow, even prevent and treat neurofibromatosis in the future. Non-pharmacological approaches are also recommended, rehabilitation, speech therapy, and psychotherapy.

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