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Therapeutic advances in treatment of patients with neurofibromatosis type 1 and type 2. 7 years clinical experience of a single centre and literature review

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ABSTRACT

Background: Neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) are rare tumoral suppressor syndromes, triggered by an abnormal mutation in a tumour suppressor gene (TSG) (1). Each of these syndromes represents an orphan disease (by itself), but the tumours encountered in these patients are the most frequent lesions of the nervous system. Between the two of these diseases, NF1 presents a greater risk of malignancy, hence the importance of an accurate diagnosis and distinction between the two pathological entities. The purpose of this paper is to describe our department's practice protocol with neurofibromatosis and review the current literature regarding clinical diagnosis and management of these complex diseases.

Methods: Our paper is a retrospective study that comprehends 25 patients with neurofibromatosis treated in our clinic between 2011 and 2018.

Results: Our study included 16 female patients (64%) and 9 male patients (36%). The mean age at presentation was 48,7 (range 14-72 years). There were 7 cases (28%) of NF1 and 18 cases (72%) of NF2. Seven cases (28%) had a positive family history and 18 patients did not (72%). The most common symptoms at presentation were hearing loss, vertigo, and headache.

Conclusions: Neurofibromatosis is a very complex disease in which the tumours may have an unforeseeable growth pattern. New tumours can grow over the years and the symptoms are unpredictable. Surgical treatment is best to be reserved for symptomatic tumours. Non-surgical procedures are also an important step of the treatment, but further studies are required to decide their effectiveness.

Keywords

neurofibromatosis,
tumoral suppressor
syndromes,
lesions of the nervous system



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BACKGROUND

Neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) are rare tumoral suppressor syndromes, triggered by an abnormal mutation in a tumor suppressor gene (TSG) (1). Each of these syndromes represents an orphan disease (by itself) (2) (3), but the tumors encountered in these patients are most frequent lesions of the nervous system (1). Between the two of these diseases, NF1 presents a greater risk of malignancy (4), hence the importance of an accurate diagnosis and distinction between the two pathological entities. The purpose of this paper is to describe our department's practice's protocol with neurofibromatosis and review the current literature regarding clinical diagnosis and management of these complex diseases.

MATERIALS AND METHODS

We performed a retrospective study that comprehends cases from 4th Neurosurgical Department of the "Bagdasar-Arseni" Clinical Emergency Hospital. We retrospectively reviewed the charts of 25 patients with neurofibromatosis treated in our clinic between 2011 and 2018. We only included patients who fulfilled the known clinical indicators for of NF1 or NF2. Eleven patients, who didn't fulfill all the other criteria for NF1 or NF2, were therefore excluded from our study.

RESULTS

Our study comprehends 16 female patients (64%) and nine male patients (36%). The average age at admission was 48,7 (range 14-72 years). The distribution of the patient sample based on the age group is shown in Figure 1. There were 7 cases (28%) of NF1 and 18 cases (72%) of NF2. Seven cases (28%) had a positive family history and 18 patients did not (72%). The most common symptoms at presentation were hearing loss, vertigo, and headache (Figure 2). Other signs and symptoms were seizures, lumbar pain, frontal lobe syndrome, or intracranial hypertension syndrome.

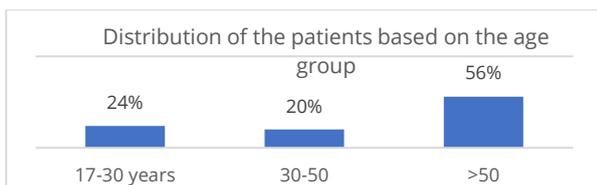


Figure 1. Age groups distribution.

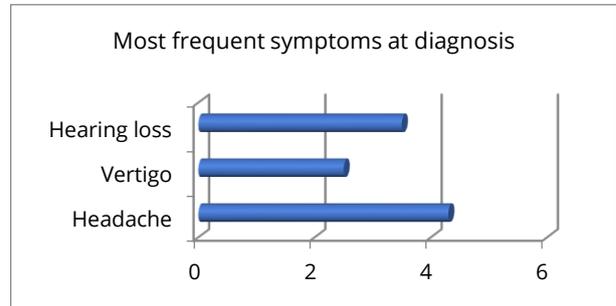


Figure 2. Most frequent symptoms at diagnosis.

In 6 cases (24%) Gamma knife radiosurgery was chosen as the first treatment option. The distribution of the tumors based on their location is illustrated in Fig. 3.

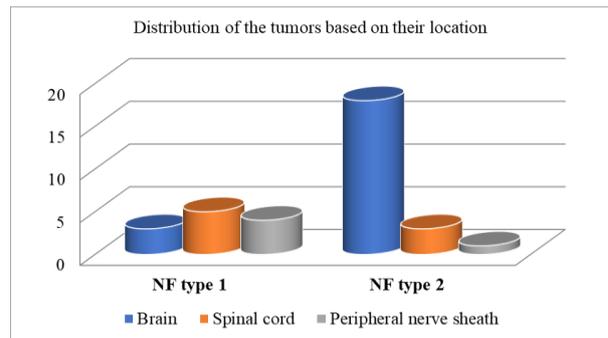


Figure 3. Distribution of the tumours based on their location in the neuroaxis.

The distribution of the patients based on whether they did, or did not, undergo surgical procedures is illustrated in Fig. 4.

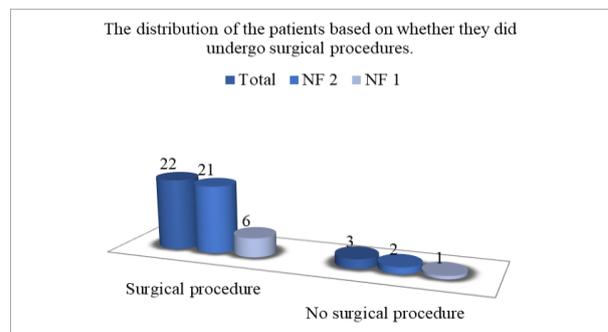


Figure 4. The distribution of the patients based on whether they did, or did not, undergo surgical procedures.

CASE PRESENTATION

We present you the case of a 14 years-old child diagnosed Type II Neurofibromatosis was referred to our clinic with a 1-year history of cervical and brachial

neuralgia, hypoesthesia, and mild weakness in her left hand, as well as numbness of the fingers and left foot hypoesthesia. Her spinal cord function was evaluated to grade D on the Frankel scale. Neurological examination revealed an increased patellar reflex, no tricipital reflexes bilaterally, left ankle clonus, and bilateral positive Babinski sign. Other clinical signs were soft subcutaneous masses (neurofibromas) on the nose, frontal and temporoparietal regions and left hand, and also axillary and thoracic café-au-lait spots.

Cervical MRI investigation revealed on the left side a massive gadolinium-enhancing extramedullary spinal tumor starting at the level of C6-C7 vertebrae, expanding into the mediastinum, displacing the vertebral artery. The tumor was also in contact with the left common carotid artery, without compression. It had a scalloping effect on the left lateral wall of the C6 and C7 vertebral bodies, entered the superior thoracic aperture and extended to the T2-T3 vertebral level (Fig. 5).

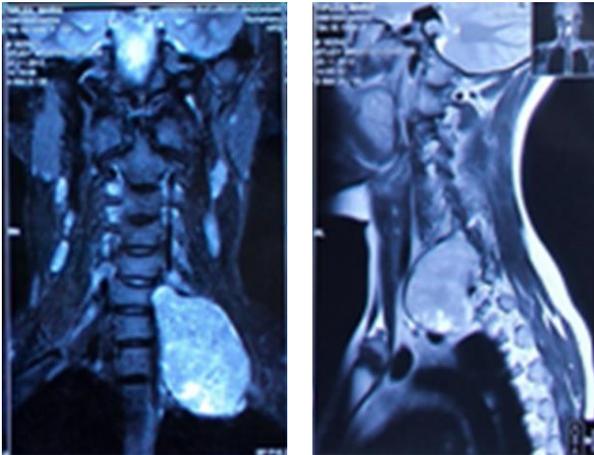


Figure 5. Gadolinium-enhanced cervical MRI, coronal and sagittal section, showing a large extramedullary spinal tumor at the level of C6-C7 vertebrae.

The patient underwent for first surgical intervention in order to excise the left medullary compressive portion of the tumor through posterior cervical approach. Six weeks later, using an anterior cervical Dartevelle approach, the extracapsular excision of the left laterocervical tumoral portion was performed. Postoperative, the patient was in good medical state, without any neurological deficit. The third intervention took place 4 weeks after and the previous one. The extracapsular excision of the tumoral process located between the right thyroid

lobe, the carotid artery and the transverse processes of C2-C5.

For the vestibular schwannoma, Gamma Knife Radiosurgery was the elective treatment. Eventually, surgical excision of the subcutaneous neurofibromas was performed.

Two years later she was referred again to our clinic with complaints of dizziness, gait instability associated with visual dysfunction, more severely right side. The cerebral MRI images revealed an expansive process of the sellar and parasellar region with temporal lobe extension (Fig. 6). Surgical intervention for total removal of the lesion was the therapeutic attitude opted by the patient. Under general anesthesia, total removal of the lesion was performed, through a right pterional approach. The histopathological examination concluded a WHO grade II meningioma. Postoperative, the symptoms from the admission were improved, without dizziness or gait instability. Visual dysfunction did not improve but the patient did not accuse the worsening of the visual dysfunction.

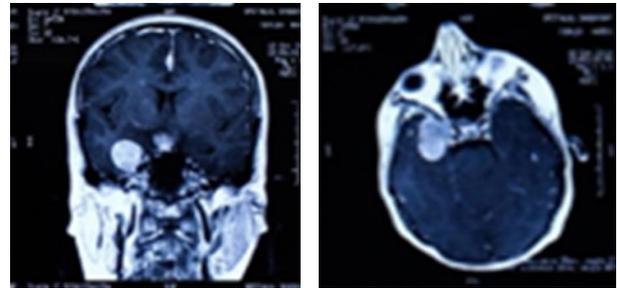


Figure 6. Cerebral gadolinium-enhanced MRI scan showing an expansive process of the sellar and parasellar region with temporal lobe extension.

The patient was strictly followed-up for early detection of new brain tumors because of their unforeseeable growth pattern. The last follow up was in February 2018 and the cerebral CT scan did not revealed any new tumour or progression of the disease.

DISCUSSION

Surgical resection represents the gold standard of treatment for plexiform neurofibromas, but the recurrence rates are significantly high (8). Targeted therapies, such as anti-Ras therapy, seem to have promising effects (9) (10). In 2020, USA Food and Drug Administration has approved the use of selumetinib for treating inoperable plexiform

neurofibromas in pediatric NF1 patients (11). Regarding treatment strategies for NF2 patients, currently there is no consensus on the effectiveness of different approaches, because of the high regrowth rate after resection (12). Surgical resection is usually guided by the clinical symptoms and the approachability of the lesion. A close clinical and imagistic follow-up is necessary in both NF1 and NF2 syndromes.

CONCLUSION

Neurofibromatosis is a very complex disease in which the tumors may have an unforeseeable growth pattern. New tumors can grow over the years and the symptoms are unpredictable. Surgical treatment is best to be reserved for symptomatic tumors. Non-surgical procedures are also an important step of the treatment, but further studies are needed in order to determine their effectiveness.

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