

Multiple primary cranio-spinal tumours in a 13-year-old female with neurofibromatosis type 2 management strategy

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Abstract

Introduction Neurofibromatosis type 2 (NF2) is an inherited, rare autosomal dominant syndrome characterised by the development of multiple benign cranial and spinal tumours, peripheral neuropathy, ophthalmological and cutaneous lesions. Herein, we report one case of NF2 treated with multivariate chemotherapy.

Material and methods A 13-year-old female presented with multiple cranio-spinal tumours in MRI. First symptoms were progressive changes in vision, left-sided paresis, unilateral sensorineural hearing loss, and left hypoglossal nerve paresis. The patient underwent palliative, partial surgical resection of the tumour which was located in a posterior fossa. Histopathological examination showed a psammomatous meningioma located near the great foramen and schwannomas of VIII nerve in the cerebello-pontine angle. Clinical and radiological examination revealed a rapid progression of the disease. As such, multivariate chemotherapy was used. The patient died 4 years after diagnosis.

Conclusion NF2 patients with multiple tumours at diagnosis may not be treatable with surgery alone and, as a result,

presentation with such a disease in childhood results in poor prognosis. The unification of management strategies in NF2 patients is highly desirable.

Keywords Children · Cranio-spinal tumours · Neurofibromatosis type 2 · Prognosis · Treatment

Introduction

Neurofibromatosis type 2 (NF2) is an inherited, rare autosomal dominant syndrome characterized by the development of multiple benign cranial and spinal tumours (schwannomas, meningiomas, ependymomas), peripheral neuropathy, ophthalmological and cutaneous lesions [1–3]. Tumours associated with NF2 are caused by the inactivation of both alleles of the NF2 tumour-suppressor gene that has been localised on the chromosome 22q12, by mutation or allele loss [1–5]. Recent evidence suggests that between 20% and 30% of NF2 cases without a family history of the disease are mosaic for the underlying disease-causing mutation and more than 50% of patients represent new mutations [4]. The disorder appears in one of 25,000 live births [1]. About 10% of NF2 patients are under the age of 10 years old. Among patients with NF2, 18% present with symptoms of the disease at the age of 15 years or less [6]. Although most tumours in the central nervous system in NF2 are slow growing, they may grow faster during childhood. In this situation, the prognosis is often poor [7]. The development of new tumours is likely in patients with NF2, even after surgery [4, 5]. In these situations, a new management strategy and early diagnosis are necessary.

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In this report, we describe the treatment of a 13-year-old female with NF2 who had multiple types of primary tumours in the brain and spinal canal.

Case report

A 13-year-old female was admitted to the Department of Paediatric Oncology because of complaints of progressive changes in vision, left-sided paresis, unilateral sensorineural hearing loss, left hypoglossal nerve paresis and difficulties in learning at school over a period of 6 months. The physical examination showed one café-au-lait spot on the left upper leg (greater than 10 cm in diameter) and one on the left scapula, schwannomas of the forearms and dysmorphic face (depressed nasal root, hypertelorism, small and downward slanting palpebral fissures, short philtrum with a tented upper lip and mandibular hypoplasia). Neurological examination revealed bilateral Babinski's reflex, left-sided muscular atrophy and a deflection of the tongue to the left. Magnetic resonance imaging (MRI) of the brain and spinal canal revealed multiple cranial nerves tumours: V-trigeminal nerve, bilateral vestibular schwannomas and right-sided meningioma, and meningioma in the area of the optic nerve (Fig. 1a, b). In the posterior cranial fossa, the huge focus involving the foramen magnum was described as schwannomas of VIII nerve (Fig. 2). Multiple spinal canal nodules, involving L5-S1 level, were observed (Fig. 3). The patient underwent palliative, partial surgical resection of the posterior fossa tumour. Histopathological examination showed psammomatous meningioma localised near the foramen magnum and schwannoma in the cerebello-pontine angle.

Following the operation, an increased paresis of lower limbs and neurogenic bladder was observed. The excision of the Th11-Th12 tumour was performed. Histopathology proved meningioma. Staphylococcus sepsis and acute renal failure were the side effects after surgery.

She finished the treatment with clinical success.

Fourteen months later, progression of the disease was stated. Bilateral deafness, facial nerve paresis, a deflection of the tongue to the right, left eye-ball oedema, visual disorders and ape hand were all observed.

She received chemotherapy (vinblastin 6 mg/m² every 2 weeks for 3 months). In the course of performing MRI of the brain and spinal canal, progression of the disease was observed. The general condition of the patient deteriorated. She was presented with difficulties in talking and severe coordination disturbances; she was unable to walk in a straight line and had lost the ability to manipulate small objects. The chemotherapy for low-grade gliomas protocol, according to the Memorial Hospital for Children in Warsaw, was administered thereafter. It was comprised of: intensive

chemotherapy–carboplatin (550 mg/m²; 1, 4, 7, 10 weeks), vincristin (1.5 mg/m², 1–10 week) and maintenance chemotherapy–carboplatin with vincristin every 4 weeks.

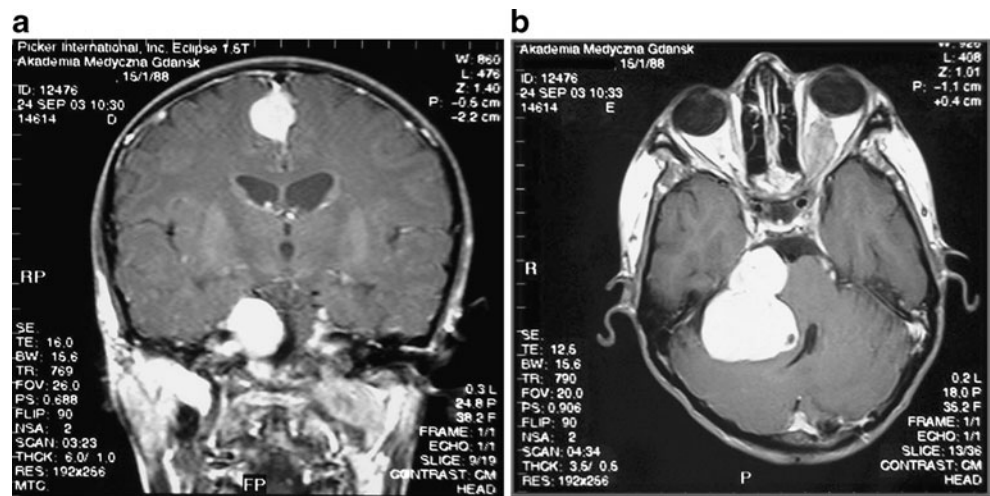
After 6 months, no response to chemotherapy was stated. Due to no possibility to remove the tumour radically, the child was included in a clinical trial. She received Irinotecan in doses of 20 mg/m² for 10 days every 3 weeks. In all, nine cycles were administered to the patient. Thanks to Irinotecan, she achieved the clinical stagnation of the disease.

Following a period of 2 years, progression of the disease was once more present. She was treated with temozolomide (150 mg/m²) for 3 months. Finally, our patient died of the progression of the disease 4 years after diagnosis.

Discussion

NF2 is an uncommon genetic disorder, which is characterized by an increased risk of benign nervous system tumour development [8]. The diagnostic criteria for neurofibromatosis type 2 is bilateral vestibular schwannomas (VS) or family history of NF2 according to first degree family relative, unilateral vestibular schwannomas under 30 years old, or any two of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract [9–12]. Nunes et al. [13], presented clinical data on 12 patients with NF2 at age before 18 years and in large number with positive family history. One third of the children had hearing impairments and two thirds presented with dysfunctions of the cranial nerve. Radiological examinations revealed cranial meningiomas in 75% of cases, cranial schwannomas in 83%, and spinal cord tumours in 75%. Evans et al. [14] showed that at least 18% of NF2 sufferers presented in childhood with isolated features of the disease had no family history. These paediatric patients presented with a more severe course of the disease with multiple tumours. In the study of Bosch et al. [15], children with early onset of the disease presented with ophthalmologic symptoms and lower motor neuron extremity weakness and in those with late disease onset, eight nerve impairment was observed. MacCollin and Mautner [16] showed that the first ocular manifestation of NF2 in the paediatric population was visual loss or diplopia. Our patient had an atypical onset of this autosomal-dominant disorder. After a few months, she presented with hearing loss, most often related to the development of vestibular schwannomas. Hearing loss, often accompanied by tinnitus, occurs in around 60% of adults and up to 30% of children [17, 18]. The MRI scan showed the presence of tumours in the central nervous system and spinal canal. In the literature, there are a great many reports confirming the variety of spinal tumours associated with NF2 [2, 19, 20]. Bilateral vestibular

Fig. 1 **a** Contrast-enhanced conventional T1-weighted MR image: neuromas of the V and VIII nerve and sagittal right-sided meningioma. **b** Contrast-enhanced transversal T1-weighted MR image: the optic nerve glioma



schwannomas are found in 90–95% of patients with NF2. It is reported that more than 99% of VS in NF2 are benign, but they remain an important cause of mortality due to their location [1]. Schwannomas can develop along the course of cranial, spinal and peripheral nerves, differently than vestibular. Most often it arises from the oculomotor, trigeminal and facial nerves [21]. Schwannomas of spinal nerves may result in discrete peripheral neuropathies. In our patient, the histopathology examination showed meningioma in the posterior cranial fossa, which is the second most common tumour connected with NF2. Intracranial meningiomas appear in 45–58% of patients with this disorder and intradural extramedullary spinal meningiomas in 20% [2]. Although meningiomas are benign, they may give clinical symptoms, the nature of which are related to their size and anatomical location. It is proven that meningiomas associ-

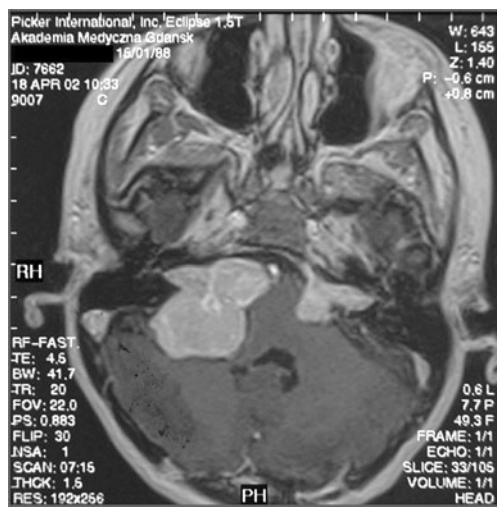


Fig. 2 In the posterior cranial fossa, bilateral pathological solid masses located in pontocerebellar cisterns, which extend to the auditory meatus; intensive contrast enhancement MR image—schwannomas of the VIII nerve



Fig. 3 Contrast-enhanced T1-weighted MR image: numerous intradural spinal canal nodules and small tumours in intervertebral foramen on the right side at level L5-S1

ated with NF2 more frequently have higher proliferative activity and a tendency to form more atypical and anaplastic grades than sporadic meningiomas [22].

The typical treatment strategy for patients with VS is “watch and wait then rescan”, complete with surgical resection and stereotactic radiotherapy. The authors noted that more than 50% of VS were stable in size, so in this situation the “watch and wait then rescan” program could be deemed the proper course [7]. Of contrary opinion is Brackmann et al. [23], regarding situations in which tumours are of less than 3 cm in diameter when early surgical management is recommended. It can preserve normal hearing in 30–65% and the functioning of facial nerves in 75–92% of patients. The role of stereotactic radiotherapy is not yet clearly determined [7].

The majority of meningiomas located in hemispheres and spinal canal can be resected safely and radically. In our patient, the location of the meningioma in the posterior cranial fossa made it impossible to remove completely. In this situation, we agreed that multi-variety protocols should be used. Due to chemotherapy, her overall survival was prolonged.

Conclusions

The prognosis in NF2 is still poor. The unification of management strategy in NF2 patients is mandatory in providing effective treatment. Integrated, multidisciplinary care consisting of a neurosurgeon, oncologist, otolaryngologist, neurologist, geneticist, ophthalmologist, pathologist and radiologist is necessary.

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