Medulloblastomas in neurofibromatosis type 1. Case report and literature review

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Summary

A 6-year-old girl, previously diagnosed with neurofibromatosis type 1 (NF-1) presented with ataxia and symptoms of raised intracranial pressure. Diagnostic work up disclosed a posterior fossa tumor. Histopathological study of the excised neoplasm showed a cerebellar medulloblastoma. We review the current literature and suggest that the association of medulloblastoma with NF-1 is not a chance occurrence, and that it might be pathogenetically related. We propose that medulloblastoma should be added to the list of malignancies that are apt to occur in NF-1.

KEYWORDS: Medulloblastoma. Neurofibromatosis type 1. PNET. Cerebral neoplasms. Chromosomal aberrations

Introduction

The neurofibromatoses are genetic disorders that affect cell growth of neural tissues. The most common type is neurofibromatosis 1 (NF-1) that is an autosomal dominant disorder affecting 1 in 3000-4000 individuals. Some NF-1 patients present with optic gliomas, or other tumors. Medulloblastoma has seldom been described in association with NF-1. We report the present case in the belief that the association of medulloblastoma with NF-1 is not a chance occurrence, and that medulloblastoma should be added to the list of malignancies that are apt to occur in NF-1.

Case report

A 6-year-old girl was admitted to hospital complaining of headaches, hypersomnia, anorexia and staggering gait for some 2 weeks. A prenatal ultrasound disclosed an ectopic right kidney. The child's delivery had been uneventful and her birth-weight was 3600 g. At the neonatal examination she was found to have more than six café-au-lait spots, larger than 5 mm. At the age of 4 she was submitted to an operation for strabismus. The child's parents were young and non-consanguineous and there was no family history of NF-1. The girl's brother, aged 13 years, suffers from rheumatoid arthritis.

On examination the girl was fully conscious and had no papilloedema. Her neurological examination was normal except for an ataxic gait. She exhibited numerous café-au-lait spots, Lisch nodules, a submucous palatine cleft, and osseous cysts due to presumed subperiostal fibromas on her left tibia. Skull radiographs showed widened cranial sutures. A computerized tomography (CT) scan demonstrated a hyperdense cerebellar tumor (Fig. 1), which was enhanced after the intravenous administration of contrast, together with a moderate degree of hydrocephalus.

On September 8, 1995, the girl underwent a posterior fossa craniectomy followed by total tumor removal. An external ventricular drainage was temporarily left in place. Histopathological diagnosis of the excised neoplasm revea-
led a classic-type medulloblastoma. The girl was treated with radiotherapy to the posterior fossa (40 Gy) and craniospinal axis (30 Gy).

The subsequent clinical and neuroimaging revisions demonstrated total tumor removal and ruled out spread of the tumor through the CSF pathways. However, at the age of 8 the girl developed symptoms of hydrocephalus and was given a ventriculo-peritoneal shunt with a programmable valve (Sophysa, France). Five years after the initial operation, the girl was asymptomatic, except for mild mental retardation, and there was no evidence of tumor recurrence or dissemination along the CSF pathways on repeat neuroimaging studies.

**Discussion**

**Neurofibromatosis I**

NF-1 is the commonest form of neurofibromatosis, and is transmitted in an autosomal dominant fashion\(^6,10\). NF-1 occurs with an incidence of 1 in 3000-4000. However, 50% of the patients have no family history of NF-1, implying a high proportion of mutations in the NF-1 gene\(^5,6,10\). The hallmark of NF-1 is the peripheral neurofibroma\(^5\). The patients may also have central nervous system gliomas, bone dysplasias, melanocytic hamartomas of the iris (Lisch nodules), and mental retardation\(^5,6,10\). The clinical criteria for the diagnosis of NF-1 has been described elsewhere\(^5\).

**Medulloblastoma**

Medulloblastoma is mainly a pediatric brain tumor that accounts for 18% of all intracranial neoplasms, and 29% of all posterior fossa tumors\(^5\). Its peak frequency is between the ages of 3 and 8 years\(^7\). The annual incidence rate is of 6 cases per million population\(^7\). There is a 6:4 male: female predominance\(^2\). Medulloblastoma is a malignant, invasive embryonal tumor that arises from the vermis and may spread to the cerebellar hemispheres, fourth ventricle and brainstem. There are two main varieties of medulloblastoma: desmoplastic and classic. The tumor may show histologic differentiation into neuroblastic or astrocytic componente, a fact that does not influence the patients' outcomes\(^2\). The most frequent presentation of medulloblastoma is with symptoms of raised intracranial pressure, which occur in 80% of the cases. Usual physical signs comprise ataxia, wide-based gait, head tilt, nystagmus, and paralysis of cranial nerves\(^3\). The findings of CT and mag-
Magnetic resonance imaging are quite specific and lead to a presurgical diagnosis in 90% of the cases. The management of medulloblastoma includes surgery and chemotherapy and/or radiotherapy in all cases.

Malignancies in NF-1

Tumors affecting the CNS in NF-1 include neurofibromas, malignant peripheral nerve sheath tumors, and astrocytomas. Non-CNS malignancies comprise chronic myeloid leukemia, pheochromocytoma, rhabdomyosarcoma, Wilms tumor, neuroblastoma, and melanoma. NF-1 is typically associated with childhood gliomas, especially of the optic pathways, hypothalamus, cerebral and cerebellar hemispheres and brainstem. The gene locus for NF-1 has been mapped at chromosome 17q11.2 that codes for neurofibromin, a protein that inhibits the ras oncogene. Some astrocytomas often show abnormalities in chromosome 17, but these anomalies are mainly in the short arm of the chromosome, which constitutes the site of the p53 suppressor gene. The mutation of a "controller" gene might lead to the development of a brain tumor. This possibility is especially increased if one copy of the gene is abnormal, as occurs in NF-1. Anomalies of chromosome 17 have also been found in medulloblastoma, although recent research suggests that this locus is different from the p53 suppressor gene.

Medulloblastoma and NF-1

Some familial cases of medulloblastoma have been reported, what suggests a genetic influence on its development. Medulloblastoma can also occur in germline deletion syndromes, such as Turcot's syndrome (APC gene), Gorlin's syndrome (Patch gene), Li-Fraumeni syndrome (p53) and Rubinstein-Taybi syndrome (CBP gene). In 1262 patients with medulloblastoma, 20 patients (1.6%) developed a second malignancy, thus indicating that the population of patients with medulloblastoma is at increased risk of developing a second tumor.

In 1969 Corkill and Ross documented a patient with NF-1, medulloblastoma, neurogenic sarcoma and a radiation-induced thyroid carcinoma. Pascual-Castroviejo et al. reported one case of medulloblastoma among 33 patients with CNS tumors within a group of 174 individuals affected by NF-1. This association was also mentioned by Meadows et al. Robles-Cascalier et al. reported a 1-year-old boy with NF-1 and a cerebellar medulloblastoma. Perilongo et al. have also reported a 6-month-old girl with a Wilms tumor who subsequently developed a medulloblastoma and leukemia. All of these cases, and our report, suggest that medulloblastoma, a tumor of primitive neuroectodermal lineage, is apt to occur in the setting of NF-1, given that the neurofibromatoses are disorders which primarily impair cell growth of neural tissues. The known propensity of NF-1 patients to develop CNS- and non-CNS tumors supports the view that the association of medulloblastoma and NF-1, although uncommon, might not be a chance occurrence and that, on the contrary, yet unknown genetic abnormalities might account for this association.

Conclusion

According to the current literature and in view of the present knowledge on cyogenetics and molecular biology of cerebral tumors, the association of medulloblastoma with NF-1 might not constitute an incidental occurrence. We suggest that medulloblastomas should be added to the list of brain tumors that are apt to develop in patients diagnosed with NF-1.

References

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