Two girl patients with medulloblastoma. Case reports

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Abstract

In childhood, the most common type of brain tumors is medulloblastoma, a highly malignant primary brain tumor that is found in the cerebellum or posterior fossa. The tumor mass increases and generates obstructive hydrocephalus. Risk factors (that might be involved in some cases) include the genetic syndrome such as type 1 neurofibromatosis, exposure to ionizing radiation and Epstein–Barr virus. Medulloblastoma is associated with recessively inherited Turcot disease and with conditions as ataxia–telangiectasia syndrome in several cases. The authors presented two cases of female patients (aged one year and eight months old, respectively 4-year-old), both of them with weight deficiency, with personal history of head trauma. First case, M.D.M., was admitted in Emergency Room of the Emergency County Hospital, Craiova, Romania, for symptoms that included headaches, impaired vision, vomiting, mental disorders, ataxia and body imbalance. The reason for refer to the Surgical Unit care was posterior fossa tumor diagnosed by computed tomography (CT) scan. The second case, V.F., a 4-year-old girl, was admitted to First Pediatrics Clinic of the same Hospital, on October 2014, for seizures, early morning vomiting, loss of appetite, inability to walk and stand also, mental delay. She had “café au lait” spots on her trunk, suggesting type 1 neurofibromatosis. A brain CT scan revealed a tumor being developed in the fourth ventricle (in the vermis of the cerebellum). Both the girls underwent curative surgery in different Clinics from Bucharest. The two girls with the same diagnosis showed contrasting post-surgical evolution: M.D.M. still survives, while V.F. survived only for six months following first surgical intervention. The first patient, M.D.M., received chemotherapy before and after the surgery, which a slow but favorable recovery noted. For the second patient, the brain CT scan performed four months after surgery showed multiple masses in the cerebral posterior fossa, suggestive of leptomeningeal metastases, but without local recurrence of the medulloblastoma. The patient started chemotherapy and, after two sessions, she went for second surgical treatment. Six months after the second surgery, the second female patient, V.F., died. The objective of this study is to find the reasons of their different clinical evolution. The authors emphasized the clinical similarities of the patients, both being female, having similar symptoms and incidental medical events (upper and lower respiratory tract infections and head trauma) but most important, they stressed out the factors which contributed to the different clinical outcome, the second patient having a more aggressive form of medulloblastoma and receiving chemotherapy only after leptomeningeal metastases were evidenced. In addition, as for the second patient, she might had clinical criteria for type 1 neurofibromatosis (the author specified the number of the “café au lait” spots being over 6, like her brother, mental delay, without other clinical signs), which might have contributed to the poor outcome. The etiology of medulloblastoma can also be involved with chromosome 17 and the diagnosis of such a brain tumor can be an evolutive criterion for neurofibromatosis. The diagnosis can provided only by genetic tests. There is a vital risk and a reason for the lethal evolution of V.F. patient. As medulloblastoma is a very aggressive malignant tumor, the approximate cumulative survival rate for preschool age group having a histological follow-up was found to be 47% over a span of five years of rigorous treatment.

Keywords: medulloblastoma, brain tumor, neurofibromatosis.

Introduction

The most frequent solid cancer in children is represented by malignant brain tumors, the medulloblastoma being the most common subtype with high-grade malignancy. Brain tumors occur at a rate of 2.5–4 per 100 000 at-risk children per year. Of these, approximately 18% are medulloblastoma. In the children population, medulloblastoma is the most common malignant brain tumor accounting for 10–20% of primary central nervous system (CNS) neoplasms and approximately 40% of all posterior fossa tumors [1]. It can also be called infratentorial neuroectodermal primitive tumor (INPT). These kinds of INPT are invasive and have a rapid growth in the brain level. The medulloblastoma is a tumor with high rate of malignancy, which is developed on the cerebellum in the posterior fossa. Because of their rapid growth and invasion of the fourth ventricle, medulloblastomas often complicate with obstructive hydrocephalus.

Medulloblastoma is a highly invasive embryonal neuro-epithelial tumor that has a tendency to disseminate throughout the CNS early in its evolution [2]. The clinical signs and symptoms are: headache, seizures, blurred vision, vomiting and abnormal behavior. The positive diagnosis is based on imaging and histological results, and it is necessary to have the immunohistochemical tests to decide the chemotherapy conduct. There are several genetic...
condition associated with medulloblastoma, as Gorlin–Goltz syndrome, Turcot syndrome, Von Hippel–Lindau disease, familial adenomatous polyposis (FAP), but several cases were described in the literature suggesting the association between medulloblastomas and type 1 neurofibromatosis. In addition, other environmental factors, like ionizing radiation exposure and Epstein–Barr infection, were found to be involved into medulloblastomas development [2–5].

The aim of our paper is to present the two clinical cases with the same diagnosis, to make a comparison in terms of symptomatology, treatment and evolution, and to identify the factors that lead to a different evolution in each patient. The study was a prospective one and the patients were diagnosed by the authors of the article. Their evolution was recorded in their follow-up visits as well as in their discharge notes. The medical data of two girls diagnosed with medulloblastoma will be the focus of this presentation.

Case presentations

Case No. 1

M.D.M. patient, aged one year and eight months old, was diagnosed in the Emergency Room of the Emergency County Hospital, Craiova, Romania, on May 15, 2014, having multiple signs and symptoms, such as: balance disorders, ataxia, apathy, vomiting and anorexia. These symptoms persisted for 4–5 months. The medical history revealed that her grandmother was suffering from genital neoplasia. From the personal physiological history, we could find that this child was born prematurely (weight 2300 g), Apgar score 8, with a favorable postnatal evolution, the child being also hospitalized with pneumonia at the age of eight months. It could be noticed that the girl had a delayed body mass index (BMI) (weight 10 kg and height 74 cm). Also, the child was affected with head trauma a few months ago. At the same day of diagnosis of brain tumor, established by computed tomography (CT) scan in the Emergency Room of the same Hospital, M.D.M. patient was referred to “Bagdasar–Arseni” Emergency Hospital, Bucharest, Romania, being hospitalized between May–June 2014. Cancer biopsy, which revealed “medulloblastoma” was followed by her surgical treatment. Her entirely diagnosis was: “desmoplasic medulloblastoma in posterior cerebral fossa, ventriculo-peritoneum shunt, secondary internal hydrocephalus; ponderal hypotrophy, secondary anemia”.

On histopathology (Figure 1), the tumor had the classical aspect of a medulloblastoma, meaning that it was composed of sheets of uniform small cells with a high nuclear/cytoplasmic ratio, with round and hyperchromatic nuclei, sometimes with pleomorphism, separated by a discrete collagen meshwork.

Figure 1 – Neuropathological features of M.D.M. patient: (A) Areas of packed small round undifferentiated cells with moderate pleomorphism surrounded by loose connective tissue bundles (HE staining); (B) A higher proliferative activity is present in dense cellular fields (Ki67 immunostaining); (C) Higher density immunexpression of p53 in tumor areas; (D) Dedublated and thickened blood vessels in highly pleomorphic tumor areas (CD34 immunostaining). All images are ×200.
The MIB-1 proliferative index was less than 50% of the tumor cells, which were also negative for neurofilaments and synaptophysin. Also, an intense positive reaction to the anti-p53 antibody was observed. A scant glial felt work was identified by the anti-glial fibrillary acidic protein (GFAP) antibody, and there was no lymphocytic infiltrate between the tumor areas or within them. The intratumoral blood vessels were not very dense, and had a tortuous appearance with variable calibers. The histopathological diagnosis was “nodular desmoplasic medulloblastoma”. Microscopically, the tumor was expanding in the subarachnoid space, as well.

Outcome for M.D.M.: On July 2014, the patient started receiving polychemotherapy treatment within the Department of Pediatric Oncology, “Fundeni” Hospital, Bucharest. Between January 5–January 12, 2015, the patient was hospitalized in the Department of Oncohematology, Emergency County Hospital, Craiova, to continue chemotherapy treatment. The patient started responding well to the treatment and the only adverse reaction was the thrombocytopenia. She also survived a varicella in 2016. She was alive in 2017 and in real wellness.

Case No. 2

The second patient, V.F., aged 4-year-old, presented on October 2014 the following symptoms: febrile seizures with morning vomiting, balance disorder, anorexia, weight stagnation and ataxia, whose onset was one month before the admission. The patient was admitted in the First Pediatrics Clinic, Emergency County Hospital, Craiova, for pneumonia with respiratory deficiency, because she had also presenting cough, fatigue, fever.

She was the second child of a young family, born as a term baby, without any pathological signs, with the weight of 2800 g. The medical history showed a head trauma in the last six months, frequent upper respiratory tract infections, and also afebrile seizures. The patient V.F., at 4-year-old, had weight 13 kg, height 89 cm and mental retardation. She had “café au lait” spots on her trunk, suggesting type I neurofibromatosis.

A brain CT scan performed in the First Pediatrics Clinic of the same Hospital revealed a tumor being developed in the fourth ventricle (in the vermis of the cerebellum).

The second girl underwent curative surgery in a different Clinic: “Maria Skłodowska Curie” Emergency Children’s Hospital, Bucharest.

The diagnosis was performed within Department of Pediatrics, Emergency County Hospital, Craiova, by CT scan, and also a cerebrospinal magnetic resonance imaging (MRI) was performed within “Maria Skłodowska Curie” Emergency Children’s Hospital, Bucharest. From the results, it could be found that a tumor mass was developing in the vermis at a hyposignal T1 and T2, intratumoral cystic areas, uneven absorption of the contrast substance, dimensions 41/46/45 mm obstructive hydrocephalus (Figure 2).

Histopathologically (Figure 3), this case presented a more desmoplastic variant of medulloblastomas, with more highlighted bundles of collagen between the tumor islands.

The tumor was also mainly pleomorphic, and immunohistochemistry revealed a higher MIB-1 proliferative index (approx. 60%), as well as a higher p53 expression. The tumor cells were positive for synaptophysin, negative for neurofilaments, with only scattered cells being positive for GFAP, and inconclusive for an anti-INI-1 antibody. Again, no lymphocytes could be identified by usual Hematoxylin–Eosin (HE) staining or by immunohistochemistry. The histopathological and immunohistochemical data were suggestive for a diagnosis of medulloblastoma with desmoplastic areas, with high histological aggressiveness, and was concluded as a nodular medulloblastoma/desmoplasic IV degree by World Health Organization (WHO) Classification of Tumors. For histopathology, paraffin-embedded tissue fragments were sectioned and first stained for routine HE, with consecutive sections being utilized for immunohistochemistry. Immunohistochemical reactions were performed using the EnVision amplification system (Dako, Redox, Bucharest) and 3,3'-diaminobenzidine tetrahydrochloride (DAB, Dako) for the signal visualization, as chromogen. Briefly, after antigen retrieval in citrate buffer pH 6, the sections were incubated in 1% water peroxide to block the endogenous peroxidase activity, blocked in skimmed milk for inhibiting unwanted antigenic false positivity, and incubated overnight with the primary antibodies: GFAP (code Z0334, 1:30 000 dilution, Dako), synaptophysin (code M0776, 1:20 dilution, Dako), neurofilament-H (NF-H, code ab8135, 1:300 dilution, Abcam), CD34 (code M7165, 1:100 dilution, Dako), CD3 (code M7254, 1:100 dilution, Dako), and CD20 (code M0755, 1:100 dilution, Dako). To validate the reactions, we use external negative (by omitting the primary antibody) and positive (brain tissue) controls. After counterstaining with Hematoxylin and coverslipping, the slides were photographed using a Nikon Eclipse 55i microscope equipped with a 5 Mp cooled charge-coupled device (CCD) video camera and the Nikon NIS Elements software.

The postoperative evolution of V.F. patient (after the first surgery) was favorable, without any fever, and with neurological balance. The post-surgical CT examination did not call for any attention regarding the tumor tissue or hemorrhage. The chemotherapy was required, but it was delayed by the family. The imagistic evaluation, after five months (CT, then MRI), revealed multiple leptomeningeal metastases in the posterior fossa (two of them were 3 cm and one was 1.5 cm in diameter). They were observed at MRI, without any local recurrence. The
evolution in V.F. patient started to get worse progressively. She attended two chemotherapy sessions, followed by the second surgical treatment, but she had postoperative hypercoagulation syndrome. Unfortunately, due to presence of metastases, she died six months after the first intervention.

Figure 3 – Neuropathological features of V.F. patient: (A) Areas of densely packed small round undifferentiated cells with moderate pleomorphism (HE staining); (B) Moderate proliferative activity is present in dense cellular fields (Ki67 immunostaining); (C) Medium density immunoeexpression of p53 in tumor areas; (D and E) Tumor fields do not contain infiltrated T- and B-lymphocytes (CD3 and CD20 immunostainings); (F) Relative low vascularization of the tumor areas (CD34 immunohistochemistry). All images are ×200.

Discussion

Both patients had weight hypotrophy and each of them suffered head (brain) injury the previous year. They were both diagnosed with medulloblastoma complicated with internal hydrocephalus and were surgically treated (for M.D.M. patient – a ventriculoperitoneal shunt was placed). The first patient, M.D.M. (at 2-year-old, weight 12.5 kg, height 98 cm) although was prematurely born, she was taken care by the family. After the surgical treatment, she grew within the limits of her age. She was operated correctly after the exploratory biopsy. M.D.M. patient is still alive in 2017, three years after the surgery. Although she had varicella, she was fully recovered. Weekly, white blood cell counts are necessary during radiotherapy and chemotherapy, as well as investigations
Regarding liver function, electrolytes, renal function, and a hearing test before each cycle of chemotherapy and again at the end of treatment.

V.F. patient had “café au lait” spots on the skin, specific for type 1 neurofibromatosis (NF) and mental delay. Her father had pigmentation patches and spots, and her little brother had similar spots like V.F.

For NF, she met five out of six criteria (the presence of the malignant tumor was the fifth): the curvature of the spine was present, visual disturbances, without neurofibromas. Type 1 NF has a variable phenotypic expression that includes skin abnormalities. Some patients may have a primarily cutaneous expression, while others may have life-threatening or severely disfiguring complications [3, 6–10].

The seizures without fever were due to the tumor, and not because of a pre-diagnosed epilepsy as shown in NF. The short postoperative survival and lack of funds did not allow the genetic examination of V.F. patient.

The changes in the chromosome 17 were recorded in several patients diagnosed with medulloblastoma. The rate of spontaneous mutation in NF-1 gene is 50%. Thus, type 1 NF is caused by the mutation in neurofibromin 1 level (17q11.2) suppressor gene for tumor. This explains the presence of the malignant tumor in the type 1 NF criteria. However, it is not well established the association between neurofibromatosis and medulloblastomas. There are several case reports in the literature, but with no significant clinical-pathological correlation until now.

Transcriptome profiling studies of medulloblastomas have recently led to a consensus to divide them into three main groups: (i) wingless (WNT)-activated medulloblastomas, (ii) sonic hedgehog (SHH)-activated medulloblastomas and non-WNT/non-SHH medulloblastomas [5].

Most of the WNT medulloblastomas are sporadic, usually resulting from mutations of the CTNNB1 gene, which encodes for beta-catenin, but with other mutations also being described [11]. Usually, these tumors have a classical medulloblastoma morphology, and only very rare anaplastic features have been described [12].

Abnormal p53 accumulation can be detected in a few cases of medulloblastoma, especially associated with cytological atypia, and further genomic and transcriptomic studies on these cases led to their stratification as typical or atypical medulloblastomas [5].

Most of the non-WNT/non-SHH medulloblastomas are more pleomorphic and anaplastic compared to the previous two types [12].

Despite of the aggressive treatment for medulloblastoma, the survival rate over five years does not exceed 47% [13]. In this study, only one of the two patients survived. The treatment for this disease often results in significant endocrinology and intellectual sequelae [14].

Conclusions

The purpose of this paper, as stated by the authors, is to highlight the factors that contribute to the poor prognosis and evolution of medulloblastomas in children aged one to five years old.

Both studied patients were detected with brain tumors in a CT scan with contrast substance and the location of the tumor was the posterior fossa tumor in M.D.M. and vermis tumor in V.F. The similarities between the two clinical cases (other than the medulloblastoma diagnosis) are: age between one and five years old, female gender, nutrition deficiency, cerebral trauma in recent past medical history, lower respiratory tract infections and poor immunity.

The differences were particularly given by the different therapeutic conduct and the clinical course adapted to each patient, and the particular location of the tumor: in the vermis and in the posterior cerebral fossa, respectively.

The patient with lethal evolution was 4-year-old, but the potential type 1 NF condition with mental retardation and delayed somatic development decreased the chances for survival. She was operated with incomplete tumor resection without prior biopsy. The malignant tumor diagnosis was established by histopathological examination of the resected piece of tissue in 14 days postsurgery, also the parents had delayed the chemotherapy treatment.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Laura Daniela Marinău, Cristina Elena Singer and Cristian Meseţină equally contributed to the manuscript and thus share the first authorship.

References


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