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Multidisciplinary management of cervical neuroblastoma in infants

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ABSTRACT

Objectives: Neuroblastoma is the most common malignancy in infancy, it is a histologically and genetically heterogeneous tumor, the therapy and outcome of which is influenced by age, histological variant and genetic background as well.
Methods: We present two consecutive infant patients with neuroblastoma of the neck discussing the etiology, the diagnosis and the surgical and oncological treatment of the tumor, which was observed in a relatively rare manifestation in the head–neck region.
Results: Our first patient (age: 5.5 months) was MYCN (v-myc myelocytomatosis viral related oncogene, neuroblastoma derived) negative, INSS (International Neuroblastoma Staging System) Stage 3 and INRGSS (International Neuroblastoma Risk Group Staging System) Stage 3 because of the contralateral lymph node involvement while the complete gross resection of the primary tumor mass was feasible. The patient is tumor free after three years of follow-up. Our second patient (age: 5 months) was MYCN negative, INSS Stage 2 and INRGSS Stage 1, as both the primary tumor and the ipsilateral lymph nodes were totally removed via a modified radical neck dissection. The patient is tumor free after three years of follow-up.
Conclusion: For MYCN negative patients, especially in early age, the prognosis of neuroblastoma is good, surgical resection and chemotherapy together is an adequate treatment protocol (as in our two patients). While MYCN-amplified patients require a combined and aggressive treatment with surgery, chemotherapy, radiotherapy, and immunotherapy to be able to obtain a favorable survival rate according to the literature.

1. Objectives

Neuroblastoma is the most common malignancy in infancy, accounting for just more than 30% of infantile cancers. Median age at diagnosis is 15 months, with most neuroblastoma patients presenting before they reach 6 years of age. In childhood, neuroblastoma accounts for approximately 8% of malignancies, only leukemia, central nervous system tumors, and lymphoma occur more frequently. Mean age of patients is 2 years, one third of the patients are diagnosed before the first year of age, two third of them are diagnosed before the age of five. The incidence of the disease among children under fifteen is 10.5/1 million/year. Localization and histopathological characteristic may vary. It may occur anywhere along the sympathetic nervous system; abdominal (adrenal) appearance is the most frequent. In childhood the adrenal and the disseminated form is common. The disease metastasizes via lymphatic and hematologic dissemination to lymph nodes, liver, bones and skin [1,2].

In infants cervical and cervico-thoracic localization is frequent: incidence of primary cervical neuroblastoma is less than 5% of all neuroblastomas, while the incidence of cervico-thoracic form accounts for less than 3% only. Cervical neuroblastoma develops mainly from the superior cervical ganglion of the sympathetic chain, which is behind the internal carotid artery [3,4]. The tumor may invade the cranial nerves IX–XII, and extend to the base of the skull. Cervical neuroblastoma presents as a palpable, multiple, indolent mass on the neck. Clinical symptoms of the disease are respiratory manifestations from snoring to severe respiratory distress, dysphagia and food aspiration due to compression of the pharynx and Horner's syndrome, which can be helpful in the diagnosis [4,5].

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Infant neuroblastoma tends to regress spontaneously; 60 percent of neuroblastoma cases regress and/or differentiate before the first year of age [1]. The overall five-year survival rate of cervical neuroblastoma is around 90% [4,5].

2. Methods

We present two consecutive infant patients with neuroblastoma of the neck discussing the etiology, the diagnosis and the surgical and oncological treatment of the tumor, which was observed in a relatively rare manifestation in the head–neck region.

Both infants under one year of age developed a multiplex, right-sided mass on the neck, which grow rapidly and dislocated the vital vessels and nerves on the neck. Because of the extent of the disease, the rapid progression, the ultrasonography and the MRI (magnetic resonance imaging) image data, suspicion of a malignant tumor arouse. Together with the elevated NSE (neuron specific enolase) serum levels the diagnosis of neuroblastoma could have been suspected even without biopsy and preliminary histopathological examination.

MYCN amplification was examined by fluorescence in situ hybridization (FISH – MYCN/LAF (2p23/2q11), LAF 2q11 as reference signal).

We decided on surgery as a primary treatment considering the young age and the stage of the disease in both infants. Histopathology revealed neuroblastoma in both cases, so the patients received chemotherapy according to the International Society of Pediatric Oncology, SIOP – neuroblastoma protocol at the Pediatric Department. The protocol was administered as shown in Table 1.

Our first patient was a 5.5-month-old girl, who developed a rapidly growing multiplex tumorous mass on the right side of the neck accompanied by Horner's triad, which could be attributed to either compression of the X cranial nerve by the tumor mass, or its origination from the sympathetic nervous system (Fig. 1). MRI showed an extensively growing malignant tumor (Fig. 2), so a modified radial neck dissection was carried out, during which we found a multiplex tumor with several metastatic lymph nodes, which was not an infiltrative type, in spite of the threatening preoperative radiological images the tumor mass could be totally dissected from the dislocated vital vessels and nerves (Fig. 3). Histopathology revealed poorly differentiated neuroblastoma with the absence of MYCN amplification (CD99: negative, Synaptophysin: strong cytoplasmic positivity, S-100: slight positive reaction, Ki-67: 70–80% proliferation fraction). The infant patient received chemotherapy (SIOP – neuroblastoma protocol, Table 1): 4 cycles (2 cycles Cyclophosphamide and Vincristin + 2 cycles Carboplatin and Etoposid). 7 weeks after chemotherapy local recurrence of the tumor on the contralateral side occurred, which was removed again surgically and 1 course postoperative chemotherapy was administered again (SIOP protocol, Table 1). Control MRI scans one and two years after treatment showed only a few normal lymph nodes on the neck. Horner's triad also improved continuously during the follow-up period. The patient is tumor free after three years of follow-up. Tumor stage was INSS Stage 3 and INRGSS Stage 3.

Our second patient was a 5-month-old girl with hypotonic skeletal muscles and somato-mental retardation. The rapidly growing multiplex tumorous neck mass on the right side was suspected to be a malignant tumor by the MRI. A modified radical neck dissection was carried out, again surgical preparation of the large, multiplex lymphatic mass could be carried out without any complications by leaving the vital organs intact on the neck. Histopathology revealed poorly differentiated neuroblastoma with the absence of MYCN amplification (tyrosine-hydroxylase positivity, chromogranin positivity, S100: no real positive reaction). Four cycles of chemotherapy was administered according to the SIOP protocol (Table 1). In the postoperative period the patient's existing, congenital dysphagia of muscle dystrophic origin worsened temporarily, percutaneous endoscopic gastrostomy was done. Control MRI one year after the treatment did not show any recurrence of the disease. The patient is tumor free after three years of follow-up. Tumor stage was INSS Stage 2 and INRGSS Stage 1.

Table 1
SIOP chemotherapy protocol for neuroblastoma.

Days	1	2	3	4	5
Vincristine	×	–	–	–	–
Cyclophosphamide	×	×	×	×	×
Carboplatin	×	×	×	–	–
Etoposide	×	×	×	–	–

Drug administration: Vincristine 0.05 mg/kg slow bolus injection, Cyclophophamide 5 mg/kg slow bolus injection; courses are given at 14 days intervals.
Carboplatin 6.6 mg/kg in dextrose over 1 h, Etoposide (VP16) 5 mg/kg in saline over 2 h; courses are given at 21 days intervals.

3. Results

In both patients the age under one, the negative amplification of MYCN and the tumor stage suspected a favorable prognosis.

Our first case was INSS Stage 3 and INRGSS Stage 3 because of the contralateral lymph node involvement, while the complete gross resection of the primary tumor mass was feasible. The patient is tumor free after three years of follow-up.

Our second case was INSS Stage 2 and INRGSS Stage 1, as both the primary tumor and the ipsilateral lymph nodes were totally

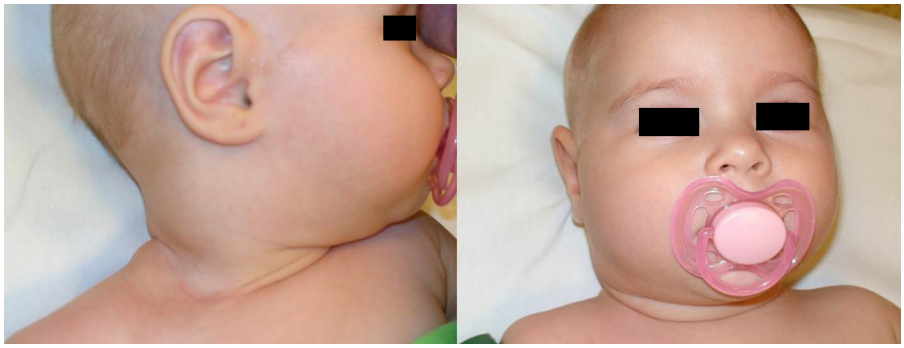

Fig. 1. Multiplex neck mass on the right side of the neck causing Horner's triad.