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Long term survival in five rare cases with multiple primary neuroblastomas

O. Brankov¹, I. Christosova², L. Marinova³

¹Department of Pediatric Surgery, University Hospital "N.I. Pirogov", Sofia, ²National Centre of Paediatric Oncohaematology, Sofia,

³Department of Radiotherapy, University Hospital "Queen Giovanna", Sofia, Bulgaria

Summary

Purpose: Multiple primary neuroblastomas are a very uncommon disorder in infancy. The tumors may arise simultaneously in different parts of the sympathetic nervous system. The purpose of this paper was to present 5 new cases with multifocal neuroblastomas. This is a representative study based on the largest clinical material in Bulgaria.

Patients and methods: The records of children treated for neuroblastoma during a 26 year-period (1979 - 2005) were reviewed and analysed retrospectively.

Results: Out of 193 children treated for neuroblastoma and followed in our department, 5 (2.6%) had multifocal lesions. All were boys aged from 2 months to 4 years at the time

of diagnosis, and all were treated successfully with radical surgery. Four children were also administered chemotherapy with vincristine, cyclophosphamide and epirubicin; one of them received postoperative radiotherapy as well. All 5 patients are alive and disease-free for a period ranging from 7 to 26 years.

Conclusion: The excellent prognosis of those rare cases with multiple primary neuroblastomas elucidates questions concerning the tumor's biological behavior and the role of different factors affecting cell differentiation, tumor growth and dissemination.

Key words: multiple primary neuroblastoma, synchronous/metachronous malignancies

Introduction

Neuroblastoma remains one of the most frequent embryonic tumors in childhood [1]. As with most similar tumors, it is diagnosed mainly before the second year of life. The simultaneous appearance of multiple neuroblastomas is a rare entity [2]. There are few reports in the literature concerning primary neuroblastomas in both adrenals as well as other multiple tumors of various stages of maturity, localized in different regions of the sympathetic nervous system [3].

The purpose of this paper was to present 5 new

rare cases with multiple primary neuroblastomas. This is a representative study based on the largest clinical material in Bulgaria.

Clinical presentations

For a 26-year period (1979-2005) 193 children with neuroblastoma were treated at the Department of Pediatric Surgery and the National Centre of Paediatric Oncohaematology, Sofia. There was a great diversity of tumor localization: retroperitoneal space - 143 (74.1%), mediastinal - 38 (19.7%), neck - 4 (2%), olfactory nerve - 3 (1.6%). Five (2.6%) children had multiple primary tumors. All 5 cases were boys aged from 2 months to 4 years at the time of diagnosis.

Histological type was classified according to Shimada et al. [4,5]. The clinical staging of each tumor was classified using the criteria of Evans [6]. At the time of diagnosis serum levels of neuron specific enolase (NSE) and lactic dehydrogenase (LDH) were not elevated in all patients.

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Author and address for correspondence

Ognjan Brankov, MD, PhD
Department of Pediatric Surgery
University Hospital "N.I. Pirogov"
1606 "Totleben" 21
Bulgaria
E-mail: brankov@pedsurg.net

Case 1

A 13-month-old boy was admitted to the hospital with simultaneous tumors located in the left adrenal and the mediastinum (August 1979). A typical triad of ptosis, miosis and enophthalmus was found on the right. Because of marked superior vena cava syndrome an emergency thoracotomy was performed with complete excision of 2 well-encapsulated tumors in the posterior mediastinum. The disease was clinically classified as stage II. The other primary tumor in the left adrenal was subsequently removed by laparotomy. Histological examination of the 3 tumors revealed neuroblastoma. Postoperatively, the child was treated for a year with vincristine and cyclophosphamide. He is alive and disease-free for 26 years.

Case 2

In 1983, a 10-month-old boy was admitted with a clinically manifested abdominal mass. The tumor arising from the left adrenal was completely excised and the specimen showed neuroblastoma. The disease clinical stage was II. Postoperatively, the child was treated monthly with vincristine, cyclophosphamide and epirubicin for a year. Three years later a mediastinal mass (not evident by chest x-ray at the time of initial presentation) was diagnosed. After radical excision of the tumor (clinical stage III) the histological examination showed ganglioneuroblastoma. The patient is alive and disease-free 23 years after the initial diagnosis.

Case 3

An abdominal tumor was discovered accidentally in a 3.5-year-old boy (December 1985). Diagnostic workup showed a tumor located in the retroperitoneum and another one in the mediastinum. A transcutaneous needle biopsy of the sizeable abdominal mass was done which revealed neuroblastoma. Two courses chemotherapy with vincristine, cyclophosphamide and epirubicin were administered. At thoracotomy, total excision of the mediastinal tumor was achieved. Simultaneously, a total surgical excision of the retroperitoneal tumor, arising from the left paravertebral sympathetic chain, was carried out. Histological examination revealed mediastinal ganglioneuroblastoma (clinical stage II) and retroperitoneal neuroblastoma (clinical stage III). Postoperatively the child was treated with radiotherapy to the abdomen with total radiation dose 30 Gy (daily fraction dose 1.5 Gy), size 10 - 12 cm to the vertebral column bilaterally for preventing scoliosis, and chemo-

therapy with monthly vincristine, cyclophosphamide and epirubicin for 1.5 years.

A year later, CT and ¹³¹I-MIBG scanning showed evidence of a tumor in the right adrenal measuring 1 x 1 cm. The parents refused a third operation. Long-term follow up showed no signs of tumor progression. He is alive and well 21 years after the initial diagnosis.

Case 4

An incidental chest radiograph in a 4-year-old boy (April 1995) showed an asymptomatic mediastinal mass. After complete tumor excision (clinical stage II), histology revealed ganglioneuroblastoma. The child received 6 postoperative courses with vincristine, cyclophosphamide and epirubicin. At the time of diagnosis no abdominal imaging had been performed. Two months later, a CT scan revealed a paravertebral abdominal mass. A radical excision of the tumor was performed with histological characteristics of ganglioneuroma. He is alive without evidence of disease for 11 years.

Case 5

A 2-month-old male infant was admitted at the hospital in 1998 because of incidentally diagnosed bilateral retroperitoneal tumors. A CT scan indicated that both tumors originated from the adrenals. At laparotomy an organ-preserving enucleation of the clinical stage II tumors was carried out, and histology showed neuroblastoma. The child is alive and disease-free 7 years after surgery.

Discussion

According to Ashley [1] multiple primary neuroblastomas are a very rare entity - about 1% of all cases. The tumors may arise simultaneously in both adrenals or in different parts of the sympathetic nervous system. There are few articles concerning this problem [2, 3]. In 1978 Ashley collected and analyzed all papers published by then, regarding multiple primary neuroblastomas: Wahl and Craig (1938) observed multiple primary neuroblastomas in a case with 3 histologically distinct tumors - neuroblastoma, ganglioneuroblastoma and ganglioneuroma. In 1942 Potter and Parrish published a case of a fetus with neuroblastoma, ganglioneuroma and fibroneuroma. Gross et al. (1959), Marsden (1963), Knudson and Amorin (1966), and Chatten and Voorhess (1967) reported other cases with multiple primary neurogenic tumors.

Ashley performed a detailed analysis of the histomorphologic findings in cases of multiple primary neuroblastomas and their different locations. He emphasized the clinical evidence that the rate of neuroblastoma *in situ* in autopsied fetuses and newborns are 40-fold higher than the cases with clinically demonstrated disease as reported by Beckwith and Perrin [7]. This greater frequency in comparison to the real clinical manifestation confirms the concept for intrauterine development of the tumor, as well as its biological ability to mature. Spontaneous regression of pediatric neuroblastoma may result in maturation to a benign form of the tumor [8]. Yamamoto et al. observed in 1998 neuroblastic tumors detected by screening and established that all tumors had decreased in size or resolved spontaneously [9].

In 2000 Hiyama et al. [3] summarized the clinical data and pathologic findings of another 53 cases of multiple neuroblastomas published in the English literature between 1966 and 1999. The author reported 11 new cases with multiple primary neuroblastomas treated successfully with surgery and chemotherapy. Hiyama et al. resumed their observations that most tumors arising from multicentric loci may have low malignant potential, as well as the ability to mature or regress.

According to Zaizen et al. [10] neuroblastomas of multicentric origin might not be uniformly characterized so that the favorable treatment outcome depends on the variable histological type of the tumor. D'Angio and Evans [11] suggested that the biological heterogeneity and the possibility of simultaneous occurrence of neuroblastoma are based on multiple independent foci of disease arising separately in each patient. Only a small number of neuroblastic nodules may transform into clinically significant neuroblastomas [12].

Our report included 5 rare cases with multiple primary neuroblastomas with 100% long-term survival, consisting 2.6 % of all neurogenic tumors treated. We did not observe a family predisposition, although some examples with family history are reported [3]. Four children had metachronous and one synchronous multifocal primary neurogenic tumors. Regarding the clinical course of our 5th case we accepted the criteria of Kramer et al. [13], estimating the tumors as simultaneous development, not as distant metastasis. In all cases, each tumor was well encapsulated and easy to extirpate. They were characterized by favorable histology according to Shimada classification. Stage distribution was stage II (2 cases) and stage III (3 cases); the tumor with the highest stage was estimated as the stage of disease for each patient.

In our study, normal levels of the tumor markers indicated the favorable characteristics. Only 2 children were under 1 year of age, which is considered to be most predisposed to spontaneous tumor regression or maturation [14]. The 2-month-old child (case no. 5) underwent only tumor extirpation as required by the principles of risk-based treatment [15]. In case no. 4 of our series (a 4-year-old boy), both tumors were well differentiated, which supports the possible process of maturation.

The incidence of multifocal neuroblastomas is likely to increase because of improved prenatal diagnosis and mass screening [3]. Diverse options for the low malignant potential of the tumors are noted. Ambros et al. [16] clarify the possible biological and genetic mechanism of spontaneous regression of neuroblastoma, stressing the role of proliferating Schwann-cells into the tumor stroma. In our series, all histological specimens had a variable cell differentiation and were characterized by favorable histology according to Shimada classification [5]. We speculate that this fact is an indication for tumor maturation and restricted growth. The prognosis of those patients is excellent due to the favorable biological behavior of the tumors. Radical surgery and appropriate chemotherapy achieved long-term tumor-free status in our series.

Conclusion

According to our observations and the relevant literature, the long-term clinical results in young children with multiple primary neuroblastic lesions are excellent. The analyzed 5 cases are interesting in many aspects. They clarify questions concerning the biological behavior of the tumor cells, tumor growth and maturation. The established variable cell differentiation of those synchronous malignancies confirms the hypothesis for a possible spontaneous regression of some malignant neuroblastomas into their benign variant.

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