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METICULOUS WAIT-AND-WATCH ATTITUDE AS A POSSIBLE THERAPEUTIC APPROACH FOR INFANTS WITH SMALL ADRENAL NEUROBLASTOMAS. A CASE REPORT OF TWO CHILDREN AND REVIEW OF LITERATURE

ŠTĚRBA J.[1], SKOTÁKOVÁ J.[2], MAZÁNEK P.[1], ŠTĚRBA M.[3], SLANÝ J.[4]

[1]Department of Paediatric Oncology, Faculty of Medicine, Masaryk University, Brno
[2]Department of Paediatric Radiology, Faculty of Medicine, Masaryk University, Brno
[3]Intensive Care Unit, Westmead Hospital Sydney, Australia
[4]Department of Paediatrics, Faculty Hospital, Ostrava

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Abstract

Neuroblastoma is the most frequent solid neoplasm in infancy, with a retroperitoneal cystic or solid mass being a sonographic sign of the conditions. The growing use of abdominal ultrasonography during pregnancy and in the postnatal period has been leading to the discovery of an increasing number of such suprarenal masses. The optimal diagnostic and treatment approaches of such masses have not yet been determined. Here we present 2 cases of perinatal neuroblastoma, managed by watch-and-wait attitude only. In addition, a review of the literature is presented.

Key words

Perinatal neuroblastoma, Wait-and-watch attitude

INTRODUCTION

Neuroblastoma is the most common malignant tumour in infants. For all patients with neuroblastoma, age, stage, and tumour biology (such as *MYCN* copy number, DNA ploidy, type of histology) are the most important variables influencing prognosis (*1–3*). Children less than one year of age with localised tumours have a five-year survival greater than 90 %, whereas in older children with advanced disease the long-term survival is less than 30 %–40 %, despite very intensive therapy, including bone marrow transplantation and differentiation therapy (*2*).

Every effort must be focused on improving the survival of the latter group, and further treatment intensification is warranted. For younger patients with localised disease it is appropriate to test possible ways of decreasing treatment intensity, thus reducing treatment-related morbidity and even mortality. Standard

treatment is represented by immediate surgical resection – adrenalectomy along with sampling of non-adherent, adjacent lymph nodes and lymph nodes located inferior and superior to the adrenal gland. Any visible ipsilateral and contralateral nodes including paracaval, interaortocaval, and para-aortic, should be sampled for a total of about 6 to 9 nodes. This is the traditional way of treatment for localised adrenal masses (*4*). The results of population-based screening for neuroblastoma in infants demonstrated that screening infants for elevated urinary catecholamines increases the total rate of diagnosis of neuroblastoma, without decreasing the mortality from advanced-stage disease (*5, 6*). Furthermore, there are reported several surgical deaths during attempts to remove adrenal masses, discovered in asymptomatic children during screening. Significant risks associated with resection of abdominal neuroblastoma in children under one year of age, with a trend toward higher risk in younger infants are reported in the literature. Typical complications include massive haemorrhage (up to 3 %), intestinal infarction, splenic injury requiring splenectomy, intussusception, respiratory failure, major vascular injury (4 %), renal atrophy (up to 10 %), and adhesive small bowel obstruction (4 %) (*4, 7, 8*). Infants are also at higher risk of anaesthetic complication (*9*). The overall mortality for young infants undergoing adrenal surgery for tumour resection seems to be about 2 % (*3, 4*). The therapeutic strategy aiming to avoid major abdominal surgery as the primary treatment modality has been trying to decrease the above-mentioned surgical risks.

CASE REPORTS

Here we report on two small infants with neuroblastoma presenting as small adrenal masses. Both children were successfully managed by close monitoring only, and their tumours have spontaneously regressed without any surgical intervention.

Case No. 1:

A baby boy was admitted to the local hospital at the age of 10 weeks due to vomiting and mild anaemia. He was born at 38th week of gestation at a local clinic, with no perinatal complications. Maternal history was unremarkable. Family history revealed his grandmother, who underwent surgery at the age of 6 years for retroperitoneal tumour, with microscopic description compatible with the diagnosis of ganglioneuroblastoma.

Abdominal ultrasonography, originally aimed at the exclusion of gastroesophageal reflux (GER), detected a tumour in the right suprarenal space. The baby was immediately referred to a regional pediatric oncology centre. Abdominal CT scans confirmed an enhancing tumour of the right adrenal gland, of a volume of 2.8 ccm. The radiologist hypothesised a rare diagnosis of cystic neuroblastoma and an extensive metastatic workup was done. There was no elevation of tumour markers (LDH, NSE, and ferritin), the levels of catecholamines (A, NA, D) and their metabolites (HVA, VMA) were within the normal range, mRNA for tyrosine hydroxylase was negative in peripheral blood, and so was his bone marrow. MIBG I^{123} scans showed a site of a significantly higher uptake in the right suprarenal space only. A Tc^{99} bone scan showed higher uptake in the skull, the left calcaneus, and the left sternoclavicular joint, but no pathology was seen on plain radiographs. Taking into consideration the published literature and the expected low-risk features of this disease; we have chosen observation only, as the treatment of choice. During a follow-up visit 3 weeks after diagnosis, the tumour regressed to a volume of 2.1 ccm. A control CT scan 12 weeks after diagnosis showed continuous regression of the tumour

to a volume of 0.25 ccm, and no radiological abnormality on originally Tc^{99} positive sites. Recently the boy has remained clinically good, with small, non-enhancing residual radiological abnormality in the right suprarenal space 9 months since the diagnosis, and with no evidence of active disease.

Case No. 2:

Prenatal ultrasound examination reported a solid mass in the left suprarenal space. The gynaecologist at a local hospital performed amniocentesis and cytogenetic analysis revealed a normal karyotype – 46,XX. The girl was born on 39th week of gestation, Apgar score 9-10-10. Abdominal CT shortly after birth showed a tumour in the left suprarenal gland, of a volume of 7.2 ml. The levels of NSE and LDH were only slightly elevated, urinary catecholamines were within the normal range, and there was no evidence of any other organ or nodal involvement. We hypothesised a diagnosis of perinatal neuroblastoma and we chose meticulous observation only, as the treatment of choice. Following discussion with the family, more extensive metastatic work-up was planned only for the case of suspected disease progression. The tumour regressed to a volume of 4.7 ccm at the age of 3 weeks. During the next follow-up visits we saw continuous spontaneous regression of the tumour size. Recently, at the age of 1 year, there remains a non-enhancing radiological abnormality in the left adrenal gland, with a total volume of 1 ccm.

Recently, both children have been doing well, growing and developing normally.

Based on available literature information, the criteria for immediate surgery or repeated extensive metastatic workup for those patients were planned as follows:

evidence of continuing tumour growth with more than 50 % increase of the solid tumour mass detected by 2 different imaging techniques;

unequivocal and repeated increase of either vanillylmandelic acid (VMA) or homovanillic acid (HVA) values, even with stable adrenal mass, or relative increase of HVA proportion in urinary catecholamine production.

The plan was to check both children in an outpatient clinic q 3 weeks during the 1st year and q 6 weeks during the 2nd year. The visits include meticulous clinical examination, abdominal ultrasound, and urinary catecholamines for each visit. Complete blood counts and AST, ALT, bilirubin, blood urea nitrogen, creatinine levels, and neuron-specific enolase have been measured at least q 6 weeks. CT scans were repeated q 3 months.

DISCUSSION

Neuroblastoma is the most common tumour of infancy. The prevalence is about 1 case per 7000 live births. Neuroblastoma may be a microscopic in-situ tumour only, or a grossly recognisable mass. Neuroblastic nodules could be found in almost all adrenal glands of foetuses at 17–30 weeks of gestational age (*10*). The incidence of in-situ neuroblastomas is 1 out of 259 autopsies among infants less than 3 months of age. This 30fold increase in the autopsy incidence compared with the clinical incidence of the tumour indicates that involution or maturation do occur spontaneously in most infants (*11, 12*).

The growing use of abdominal ultrasonography during pregnancy and in the early postnatal period has been leading to the discovery of an increasing number of suprarenal masses. The optimal diagnosis and management of these masses have not yet been clearly determined (*13, 14*). *Holgersen* and colleagues reported a trial of expectant observation on four adrenal masses, two cystic and two solid, diagnosed on fetal ultrasound and all four masses resolved with no treatment within twelve weeks after birth. There were no recurrences after two to five years' follow-up (*15*). *Hirata* reported no tumour with an ultrasound-measured volume of less than

16 ccm (a sphere with a diameter of 3.1 cm) with the International Neuroblastoma Staging System (INSS) being a stage greater than 1 (*16*). Size thus appears to be a reasonable correlate of low stage in infant neuroblastoma.

The results of population-based screening for neuroblastoma in infants at six months of age provide further support for expectant management of fetal neuroblastomas in general. Studies performed in both Japan and Canada definitely demonstrated that screening infants for elevated urinary catecholamines increases the total rate of neuroblastoma diagnosis, unfortunately without decreasing the mortality from advanced-stage disease (*5,6*). The majority of cases detected by population-based screening were localised, biologically favourable tumours, supporting the idea that low-stage neuroblastomas in infants, and the life-threatening advanced-stage disease normally seen in children over one year of age, are probably different diseases (*13, 17–21*). Yamamoto has reported a limited observational trial with eleven patients with localised disease detected by mass screening and all tumours decreased in size during the observation period (22). The most reliable signs of tumours that are likely to progress to an advanced stage seem to be steady tumour growth, increasing urinary catecholamine excretion, and/or inversion of the urinary VMA/HVA ratio. A relative increase in HVA correlates with tumour progression (*17, 18, 20, and 23–25*). Similar results supporting the wait-and-watch attitude were reported recently by Okazaki for a group of 10 patients, where tumours regressed in 7 of them (*25*).

These findings and our own experience (despite being based on 2 infants only) in accordance with the available literature suggest that localised neuroblastomas with expected favourable biological features could be safely managed by careful observation only, with a low risk of progression to advanced-stage disease. Close co-operation among the paediatric surgeon, the oncologist, and the radiologist are essential conditions for such attitude.

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MOŽNOSTI KONZERVATIVNÍHO POSTUPU V LÉČBĚ KOJENCŮ S NEUROBLASTOMEM NÍZKÉHO RIZIKA

S o u h r n

Neuroblastom je nejčastějším maligním nádorem kojeneckého věku. Jeho prognóza je určena především věkem pacienta, klinickým stadiem onemocnění a biologickým typem nádoru. U kojenců s lokalizovaným onemocněním je prognóza příznivá. Více než 90 % dětí se dožívá 5 let po diagnóze bez známek onemocnění, zatímco u starších dětí s metastatickým onemocněním je dlouhodobé přežití bez známek choroby i navzdory velmi intenzivní léčbě dosahováno pouze u 30 % pacientů.

Pro kojence s lokalizovaným onemocněním a dobrou prognózou je tedy na místě zvažovat snižování intenzity terapie a redukovat tak nežádoucí účinky léčby. Jednou z možností je využít dobře dokumentované vlastnosti některých neuroblastomů spontánně regredovat a některé, přísně vybrané děti s neuroblastomy nízkého rizika, jen sledovat. Obvyklým postupem u dětí s lokalizovaným neuroblastomem nadledviny je stále časná chirurgická intervence. Autoři v článku prezentují kazuistiky 2 dětí, u kterých byl úspěšně použit konzervativní postup spočívající v pečlivé observaci pacientů a přehled dostupné literatury.

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