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Neuroblastoma in an infant with Down's syndrome

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Summary. *Aim:* In this study we show that Down's syndrome may be accompanied by neuroblastoma. *Patients and methods:* A 15-month-old female infant with Down's syndrome and congenital hypothyroidism was admitted to our hospital with abdominal distension. Abdomen ultrasound (US) and computed tomography (CT) revealed right abdominal mass. The level of urinary homovanillic acid was 498.2 mg/24 h (N: 2-7.4 mg/24 h), and the serum neuron specific enolase (NSE) level was 370 ng/mL (N: 4.7-17 ng/mL). Karyotyping revealed 47 XX+21 chromosome, consistent with the diagnosis of Down's syndrome. Bone marrow aspirates revealed metastatic neuroblastoma. On the basis of these findings, the patient was diagnosed with stage IV neuroblastoma. The patient was treated as stage IV neuroblastoma according to our national neuroblastoma protocol which included 4 cycles of 2 different multidrug regimens and then the mass was totally removed. After the operation, two cycles of chemotherapy were administered. However, the patient died of pneumonia. *Results:* We here describe a case of Down's syndrome associated with neuroblastoma. *Conclusions:* Neuroblastoma in Down's syndrome is extremely rare. Although children with Down's syndrome are protected by the S-100 b gene on chromosome 21, neuroblastoma can be seen in Down's syndrome.

Key words: Down's syndrome, infant, neuroblastoma

«Neuroblastoma in un bambino con sindrome di Down»

Riassunto. *Scopo*: In questo studio si dimostra che la sindrome di Down può essere accompagnata da Neuroblastoma. *Pazienti e metodi*: Una bambina di 15 mesi con sindrome di Down e ipotiroidismo congenito è stata ammessa al nostro ospedale con distensione addominale. L'ecografia addominale e la tomografia computerizzata hanno rilevato la presenza di una massa addominale destra. Il livello di acido omovanillico urinario era di 498,2 mg/24 h (N: 2-7,4 mg/24 h), e il livello di enolasi neurone specifica nel siero era di 370 ng/mL (N: 4,7-17 ng/mL). Il cariotipo ha rilevato l'assetto cromosomico 47XX+21 compatibile con la diagnosi della sindrome di Down. L'ago aspirato midollare ha rilevato la presenza di Neuroblastoma metastatico. Sulla base di questi risultati è stato diagnosticato un Neuroblastoma di fase IV. La paziente è stata trattata secondo le indicazioni di Neuroblastoma di IV stadio in base al nostro protocollo nazionale che comprendeva 4 cicli di due diversi regimi di cocktail di farmaci, seguiti dalla rimozione completa della massa. Dopo l'operazione sono stati somministrati due cicli di chemioterapia. La paziente è deceduta a causa di una polmonite. *Risultati*: Si descrive un caso di sindrome di Down associato a Neuroblastoma. *Conclusioni*: Il Neuroblastoma nella sindrome di Down è estremamente raro. Anche se i bambini con sindrome di Down sono protetti dal gene S-100 b sul cromosoma 21, il Neuroblastoma può comunque essere riscontrato nella sindrome di Down.

Parole chiave: sindrome di Down, bambini, neuroblastoma

Introduction

Down's syndrome has been shown to carry a substantially increased risk for the development of some malignancies, especially leukaemia (1, 2). However, an epidemiological study by Satgé *et al* (3) has shown that neuroblastoma is very rare in Down's syndrome. Here, we report a neuroblastoma in an infant with Down's syndrome.

Case

A15-month-old female infant with Down's syndrome and congenital hypothyroidism was admitted to our hospital with abdominal distension. Family histories were unremarkable. On physical examination, signs of dysmorphism like large tongue, slanted eyes, epicanthic folds, simian crease, short broad hand with short middle phalanx of fifth finger, right abdominal mass, 1/6 systolic murmur, and umbilical hernia were noted.

Complete blood count, urine and serum biochemical analyses were normal except for elevated lactate dehydrogenase level (4087 U/L, N: 94-192 U/L). Abdomen US and CT (Figure 1) revealed right abdominal mass measuring 126x122x90 mm. The level of urinary homovanillic acid was 498.2 mg/24h (N: 2-7.4 mg/24h), whereas the level of urinary vanilmandelic acid was normal. The serum NSE level was 370 ng/mL (N: 4.7-17 ng/mL). Karyotyping revealed 47 XX+21 chromosome, consistent with the diagnosis of Down's syndrome (Figure 2). Bone marrow aspirates revealed metastatic neuroblastoma. Histologic findings showed a neoplasm characterized by small round cells with scanty cytoplasm. Immunohistochemical investigations revealed a strongly positive reaction with neuron-specific enolase in the cystoplasm of the tumour, and negative for CD-45, CD-99, desmin, vimentin, periodic acid schiff, and S100. On the basis of these findings, the patient was diagnosed as stage IV neuroblastoma. The patient was treated as stage IV neuroblastoma according to our national neuroblastoma protocol which included 4 cycles of 2 different multidrug regimens. As induction treatments [vincristine (1.5 mg/m^2 first and fifth d), ifosfamide (1.8 mg/m^2 1 to 5 d), dacarbazine (250 mg/m^2 1 to 5 d), doxorubicin (20 mg/m^2 1 to 5 d)]; and [cisplatin (30 mg/m^2 1 to 5 d), and cyclophosphamide (300 mg/m^2 1 to 5 d), etoposide (150 mg/m^2 fourth and fifth d)] were used.

After the induction treatment, the control magnetic resonance imaging revealed a right abdom-

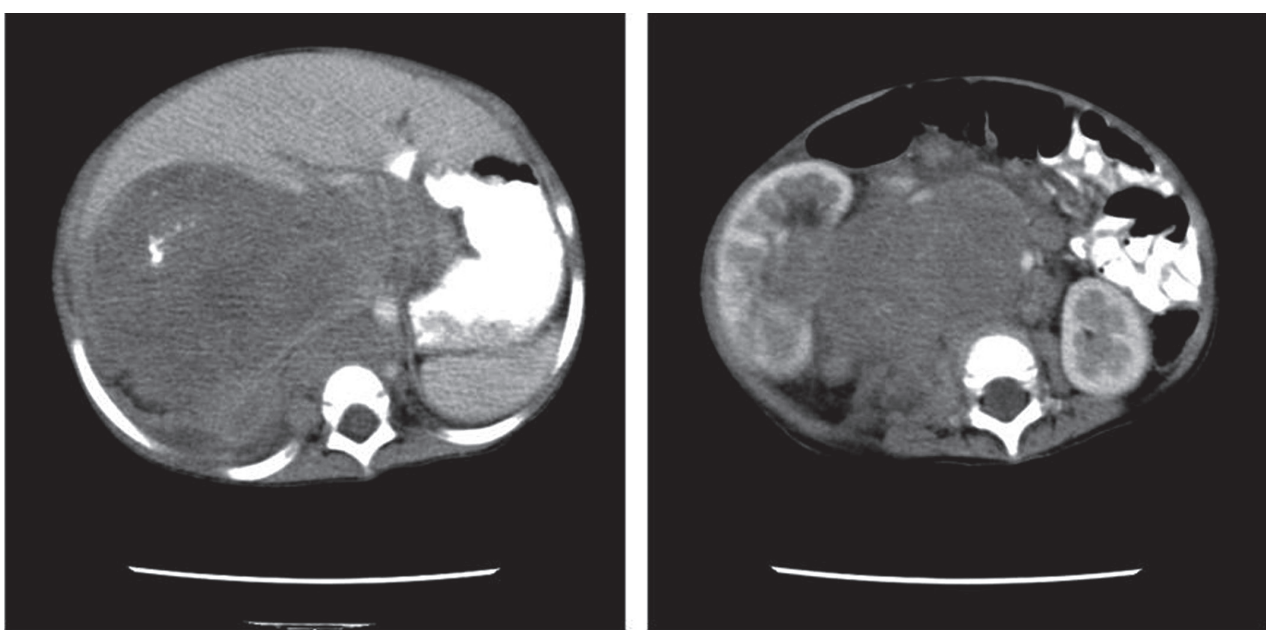

Figure 1. The abdomen CT shows right suprarenal mass

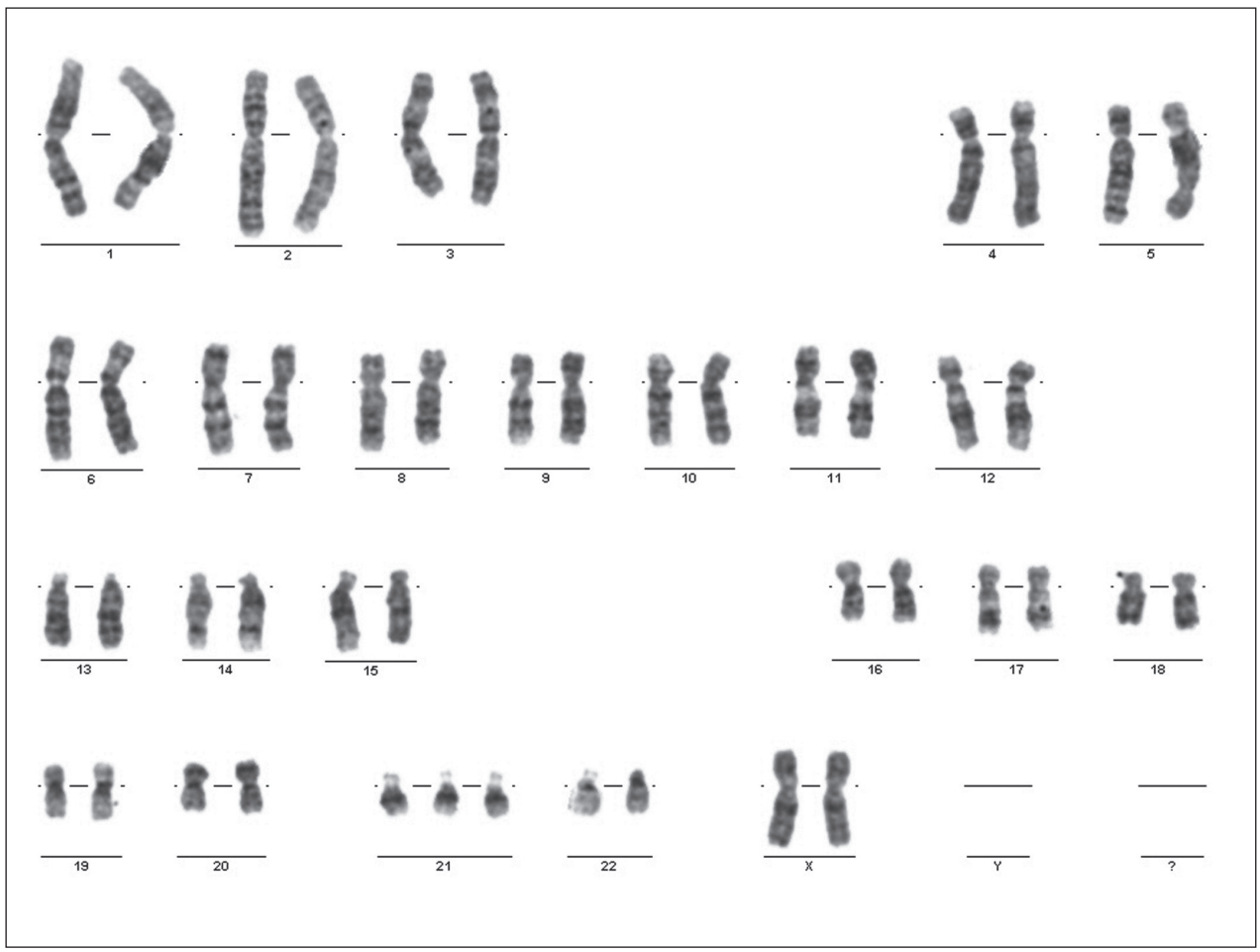

Figure 2. Karyotyping reveals 47 XX+21 chromosomes

inal mass measuring 30x25x25 mm and the mass had been removed totally. After the operation, two cycles of chemotherapy were administered. However, the patient died of pneumonia.

Discussion

Neuroblastoma is the most common extracranial solid tumour of infancy. It is an embryonal malignancy of the sympathetic nervous system arising from pluripotent sympathetic cells. Hirschsprung's disease, central hypoventilation, and neurofibromatosis type 1 have all been described in association with neuroblastoma, suggesting the existence of a global disorder of neural crest derived cells (i.e., neurocristopathy) (4-7). Also, a higher incidence of neuroblastoma has been suggested in Turner syndrome (8).

Down's syndrome is characterized by a recognizable phenotype. The high risk of leukaemia in children and a decreased risk of solid tumours except retinoblastoma, germ-cell tumours, and perhaps lymphomas in all age-groups in Down's syndrome are well-known (1, 2).

Satgé *et al* (3) conducted a study to evaluate the incidence of neuroblastoma in Down's syndrome and no cases of Down's syndrome were detected among 6,724 patients with neuroblastoma. S-100 b protein, the gene which maps to the long arm of chromosome 21, is overproduced in Down's syndrome. They emphasized that S100-b inhibits growth and differentiation of neural cells *in vitro*, is abundant in good-prognosis

neuroblastomas, and has been shown to induce growth inhibition and differentiation and cell death in several human and murine neuroblastoma cell lines, which could be responsible for this variation.

In the literature paravetabral neuroblastoma was presented in a 12 year-old boy with Down's syndrome by Koyama *et al* (9). The other patient was reported by Trebo *et al* (10). The patient was a 19 month-old boy presenting with a large primary tumour occupying both sides of the abdomen and spreading to the abdominal and the supraclavicular lymph nodes. After biopsy, neuroblastoma was diagnosed and chemotherapy and radiotherapy were performed. At the time the article was written, the patient was in complete remission.

In our case, a 15 month-old female infant with Down's syndrome and congenital hypothyroidism was admitted to our hospital with abdominal distension. During examination, a right abdominal mass was noted. Laboratory evaluation revealed high lactate dehydrogenease urinary homovanillic acid and NSE levels. Karyotyping revealed 47 XX+21 chromosome. Imaging studies revealed a right abdominal mass. Bone marrow aspirates revealed metastatic neuroblastoma. Tru cut biopsy was performed and neuroblastoma was diagnosed. The patient was treated as stage IV neuroblastoma according to our national neuroblastoma study protocol which included 4 cycles of 2 different multidrug regimens. After induction treatment, the mass was significantly smaller at control magnetic resonance imaging. After the operation, two cycles of chemotherapy were administered. However, the patient died of pneumonia.

Conclusions

In conclusion, neuroblastoma in Down's syndrome is extremely rare. Although children with Down's syndrome are protected by the S-100 b gene on chromosome 21, neuroblastoma may nonetheless be seen in Down's syndrome.

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