ABSTRACT. Background. Since the introduction of mass screening of infants for neuroblastoma, the incidence of neuroblastoma has increased in Japan. The reason for this increased incidence is the possible inclusion of many neuroblastomas that would have regressed spontaneously and would never have been detected clinically. An extremely rare tumor at the dome of the urinary bladder in a 7-month-old infant was detected by the mass screening.

Methods. A case of neuroblastoma of the urinary bladder is reported with a review of the literature. The data in the Japan Children's Cancer Registry are also reviewed to analyze the incidence and the site of origin of neuroblastoma for evaluation of mass screening.

Results. A 7-month-old female infant was referred because of a positive urine vanillylmandelic acid screening test. Ultrasonography showed a solid mass attached to the urinary bladder. At laparotomy a 35 × 30 × 25-mm egg-shaped tumor was found at the dome of the bladder, and a partial cystectomy was performed. During the operation no changes in blood pressure occurred when the tumor was manipulated. Histologic diagnosis was rosette-fibrillary neuroblastoma originating in the bladder wall, with a favorable Shimada histopathologic classification. N-myc was not amplified, which predicted a favorable prognosis, and no postoperative chemotherapy was given. The patient was free of symptoms and tumor after a follow-up period of 16 months. Literature review revealed that this was the second case of neuroblastoma of the urinary bladder ever reported in the world, although several cases of pheochromocytoma originating in the bladder wall had been reported. Both neuroblastoma and pheochromocytoma derive from the neural crest. The sympathogonia from the neural crest, a common stem cell, differentiates into a ganglion cell or into a secretory cell known as a chromaffin cell, able to manufacture catecholamines. The first case in the world that was reported as neuroblastoma of the urinary bladder was in a 4-month-old infant who was noted to have a 4-cm lower abdominal mass on routine physical examination. A ganglioneuroblastoma of the dome of the bladder was excised and the patient was doing well. On reviewing the Japan Children's Cancer Registry, the incidence of neuroblastomas in infants has increased as well as the number of stage 1, 2, and 4s (stage 4 special) neuroblastomas since the introduction of mass screening. However, there has been no significant change in the number of stage 3 or 4 diseases diagnosed in older children. According to the Japan Children's Cancer Registry, pelvic origin neuroblastoma, which has been noted to have spontaneous regression, was more frequent in the primary tumors detected by mass screening when compared with those presenting clinically. During preparation of this manuscript another case of bladder dome neuroblastoma was detected by urinary vanillylmandelic acid screening of 6-month-old infants for neuroblastoma in Japan.

Conclusion. These extremely rare cases of neuroblastoma of the urinary bladder involved children younger than 1 year of age and were incidentally detected by routine physical examination or mass screening. This raises the question of whether these tumors might have regressed spontaneously had they gone undetected and untreated. Pediatrics 1999;103(5). URL: http://www.pediatrics.org/cgi/content/full/103/5/e67; neuroblastoma, urinary bladder, mass screening.

ABBREVIATION. VMA, vanillylmandelic acid.

Since the introduction of mass screening of infants for neuroblastoma, the incidence of neuroblastoma has increased in Japan. The reason for this increased incidence is the possible inclusion of many neuroblastomas that would have regressed spontaneously and would never have been detected clinically. The purpose of this report is to describe an extremely rare tumor at the dome of urinary bladder in a 7-month-old infant, which was detected by the mass screening. Although several cases of pheochromocytomas, which, like neuroblastomas, derive from the neural crest, have been reported to originate in the urinary bladder, only one case of neuroblastoma of the bladder has ever been reported in the world literature. We report a second case and we also review the data from the Japan Children's Cancer Registry to analyze sites of origin of neuroblastoma.

CASE REPORT

A 7-month-old infant was referred for further evaluation because of a positive urinary vanillylmandelic acid (VMA) screening test. Abdominal ultrasonography showed a hypeechoic solid mass localized at the dome of the urinary bladder. The patient seemed to be healthy and the physical examination was normal except for a round mass, 3 cm in diameter, palpable at the suprapubic region. Blood pressure was normal. Computed tomography as well as magnetic resonance imaging showed that the tumor originated in the bladder wall, and a metaiodobenzylguanidine scan demonstrated abnormal uptake at the tumor (Fig 1). At the initial screening, urinary VMA and homovanillic acid excretions were 40 µg/mg of creatinine (normal, <20 µg/mg) and 27 µg/mg of creatinine (normal, <36 µg/mg), respectively. A repeat test was
again positive for VMA, which was 37 μg/mg creatinine. Serum neuron-specific enolase was 17 ng/mL (normal, <14 ng/mL) and serum lactate dehydrogenase was high (730 U/L). Blood levels of adrenalin and noradrenalin were determined twice: 135, 292 pg/mL (normal 50 – 80 pg/mL) and 257, 1640 pg/mL (normal 590 – 420 pg/mL), respectively. At laparotomy, a 35 × 30 × 25-mm egg-shaped tumor was found at the dome of the bladder. A partial cystectomy was performed, removing a 0.3-cm cuff of bladder with the tumor (Fig 2). During the operation no changes in blood pressure occurred when the tumor was manipulated. The histologic diagnosis was neuroblastoma, rosette-fibrillary type (Fig 3), with a favorable Shimada histopathologic classification, and the cells of the tumor were strongly immunostained for neuron-specific enolase. The patient’s postoperative course was uncomplicated, and her serum and urine catecholamine levels were normal. N-myc was not amplified, which predicted a favorable prognosis, and no postoperative chemotherapy was given. The patient was free from symptoms and tumor after a follow-up period of 16 months.

DISCUSSION

Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas are tumors that, like pheochromocytomas, derive from the neural crest and are located in either the adrenal medulla or in association with the sympathetic ganglia and nerves. The urinary bladder, to the wall of which small nests of paraganglionic tissue migrate with sympathetic ganglia, has been involved in 10% of the pheochromocytoma cases. The sympathogonia from the neural crest, a common stem cell, differentiates either into a ganglion cell or into a secretory cell known as a chromaffin cell, able to manufacture catecholamines. Microscopic fields of ganglioneuroma are known to occur in pheochromocytomas of the bladder. Two cases out of 40 extra-adrenal pheochromocytomas in children originated in the bladder wall, which presented a distinct symptom complex of headache, fainting, and hypertension initiated by voiding. Although several cases of malignant paraganglioma (pheochromocytoma) of the urinary bladder have been reported, only one case of neuroblastoma of the bladder has ever been reported in the world literature. This reported case was a 4-month-old infant who was noted to have a 4-cm lower abdominal mass on routine physical examination. A ganglioneuroblastoma of the dome of the bladder was excised and the patient was doing well. The second case, the subject of the present report, was detected by the Japanese neuroblastoma mass screening.

The initial experimental screening program for 6-month-old infants by urinary VMA and homovanillic acid excretions was instituted in Kyoto, Japan in 1973. Encouraging results from the study led to the introduction of a nationwide mass screening system in 1985. Since introduction of the screening, the incidence of neuroblastomas in infants has increased, as well as the number of stage

Fig 1. Metaiodobenzylguanidine scan shows abnormal uptake at the tumor.

Fig 2. At laparotomy 35 × 30 × 25-mm tumor was found at the dome of the bladder. A partial cystectomy was performed.
1, 2, and 4s neuroblastomas, as can be seen in Fig 4. However, there has been no significant change in the number of stage 3 or 4 diseases diagnosed in older children.7 According to the Japan Children’s Cancer Registry, there seems to be some difference in the site of origin of neuroblastomas detected by mass screening compared with those presenting clinically. Tumors of retroperitoneal and pelvic origin are more frequent in mass screening positive cases (Fig 5). Pelvic neuroblastomas are unusual tumors with much more favorable prognosis than abdominal neuroblastomas.8 Spontaneous maturation and/or regression has been noted to occur in pelvic neuroblastomas in infants.9 In this particular case reported herein, surgery might have been unnecessary. Now some institutes in Japan have started to adopt a wait-and-see strategy, without
any therapeutic interventions, for selected stage 1 or 2 neuroblastomas identified in infants screened at 6 months of age. A well-designed Quebec study has shown that screening has not reduced the incidence of mortality associated with high-risk neuroblastomas in older children, and concluded that widespread screening for neuroblastoma at or before the age of 6 months should not be adopted anywhere in the world.

During preparation of this manuscript, another case of bladder dome neuroblastoma was detected during mass screening at Kanagawa Children’s Medical Center (personal communication with Dr Nishihira).

**CONCLUSION**

These extremely rare cases of neuroblastoma of the urinary bladder involved children younger than 1 year of age and were incidentally detected by routine physical examination or mass screening. This raises the question whether these tumors might have regressed spontaneously had they gone undetected and untreated.

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