Maturation of Mass-Screened Localized Adrenal Neuroblastoma

By Tadashi Iwanaka, Keiko Yamamoto, Yoshihiro Ogawa, Mari Arai, Mitsuhiko Ito, Hiroshi Kishimoto, Ryoji Hanada, and Satohiko Imaizumi

Saitama, Japan

Background/Purpose: In infants, neuroblastoma has been known to spontaneously differentiate into a benign ganglioneuroma. Although several investigators have compared mass-screened with unscreened, disseminated with localized, and adrenal with retroperitoneal neuroblastoma, there are very few cross-comparisons of the above parameters. Herein, the authors report the maturation of mass-screened, localized adrenal neuroblastoma.

Methods: Fifty-one mass-screened adrenal neuroblastomas were divided into 2 groups. In infants less than 1 year of age (Group A), 45 neuroblastomas were resected, whereas 6 neuroblastomas were resected after observation in 1- to 4-year-old children (group B). Histopathology of the tumors in the 2 groups was compared. Data were analyzed by χ2 test, and P < .05 was considered significant.

Results: According to the International Neuroblastoma Pathological Classification, 41 of 45 tumors of group A were “differentiating neuroblastoma” and 4 of 6 tumors of group B were “maturing ganglioneuroma.” Maturation toward ganglioneuroblastoma was observed in 16 neuroblastomas of group A (36%) and 6 neuroblastomas of group B (100%). In group A, 58% had low mitosis karyorrhexis index (MKI); all patients in group B had low MKI.

Conclusions: If left untreated, maturation of mass-screened, localized adrenal neuroblastomas is a common phenomenon. These children do not need to undergo early operation.

INDEX WORDS: Neuroblastoma, mass screening, adrenal, maturation.

S PONTANEOUS REGRESSION and maturation is a common phenomenon of neuroblastoma detected by mass screening of 6-month-old infants. However, the frequency and phase during which this phenomenon occurs is still unclear. There are several reports on the natural course of mass-screened neuroblastomas without any therapeutic intervention, as well as on the clinicopathologic aspects of mass-screened neuroblastomas resected after untreated observation. Although most of these reports include various parameters, such as mass-screened or unscreened, disseminated or localized, adrenal or retroperitoneal neuroblastomas, there are very few cross-comparisons of the above parameters. Herein, we report our findings on 51 mass-screened, localized adrenal neuroblastomas that were resected and histologically evaluated.

MATERIALS AND METHODS

In April 1994, we started an observation program without surgery or chemotherapy for mass-screened neuroblastoma patients who met the following criteria: stage I or II tumor, tumor less than 5 cm in diameter, no invasion to the intraspinal canal or to the great vessels, urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels less than 50 μg/g creatinine, and informed consent obtained from the parents. The tumor was resected in only those patients whose neuroblastoma have been observed without any surgery and chemotherapy under the above-mentioned observation program.

RESULTS

The histopathology of 41 of the 45 neuroblastomas in group A were classified by INPC criteria as “differentiating neuroblastoma,” whereas the remaining 4 were urinary VMA and HVA at 6 months of age. Seventy-three of the 141 neuroblastomas originated from the adrenal gland, of which, 51 were determined to be stage I or II localized adrenal neuroblastoma, according to the International Neuroblastoma Pathology Classification (INPC). Forty-five of the 51 localized adrenal neuroblastomas were resected at age less than 1 year (group A), whereas the remaining 6 neuroblastomas were resected at 1 to 4 years of age (after 6 to 48 months observation periods), after untreated observation (group B; Table 1). However, 30 patients with mass-screened localized neuroblastoma have been observed without any surgery and chemotherapy. INPC-determined histologic and morphologic features of the tumors, including differentiation toward ganglioneuroblastoma and mitosis karyorrhexis index (MKI) were compared between the 2 groups A and B. Levels of urinary VMA and HVA also were obtained and evaluated in group B patients. Data were analyzed using χ2 test with Yate’s correction, and P value less than 0.05 was considered significant.
“poorly differentiated neuroblastoma” (Fig 1). In group B, 4 neuroblastomas were classified as “maturing ganglioneuroma.” Maturation toward ganglioneuroblastoma, as evaluated by the existence of ganglion cells, was observed in 16 neuroblastomas of group A (36%) and all 6 neuroblastomas of group B (100%). This difference between the 2 groups was statistically significant ($P = .003$; Fig 2). Difference in the ratio of low-MKI also was significant at 58% in group A and 100% in group B ($P$ value = .045; Fig 3). No $N$-myc amplification was observed in neuroblastomas of either group. In group B, the levels of urinary VMA and HVA gradually decreased during untreated observation, and were within the normal range by approximately 24 months of age (Figs 4 and 5).

DISCUSSION

The biological and clinical behavior of neuroblastoma is very erratic, as indicated by the spontaneous regression or maturation of some tumors but not of others.2,5 Yamamoto et al3 reported spontaneous regression of localized neuroblastoma detected by mass screening, via a no-treatment strategy of wait and see. This strategy of untreated observation of localized mass-screened neuroblastoma, without any surgical intervention or chemotherapy, has been adopted by several investigators.4,5 However, population-based studies in Canada and Japan have found that mass screening for neuroblastoma does not reduce the risk of mortality.8,9 These studies showed that mass screening increased the occurrence of neuroblastoma in infants, but it did not decrease the incidence of unfavorable advanced-stage neuroblastoma in older children. Their study population, however, included tumors of adrenal, retroperitoneal, and mediastinal origin that were either localized (stage I and II) or disseminated (stage IVS).

We believe that appropriate assessment of the usefulness of mass screening for neuroblastoma in infants can be achieved only by evaluating spontaneous regression or maturation of neuroblastoma in cases of similar disease. We sought to do this by comparing histopathologic parameters from patients that underwent early surgery (group A) with those who underwent late surgery (group B), in a mass-screened, localized adrenal neuroblastoma population consisting of 51 patients. Although there were 20 additional cases of radiologically localized adrenal neuroblastoma that had been detected by mass screening and observed without treatment, they were excluded from our study population because they did not undergo biopsy, and so could not be evaluated histopathologically.

After a certain period of observation, ultrasonography,
magnetic resonance imaging, and urinary VMA and HVA can neither confirm spontaneous regression nor deny transformation to progressive disease. Hence, our study group consisted only of those patients that appeared to undergo spontaneous maturation, which then were divided into early and late surgery groups for statistical comparison and analysis. To accurately capture the progression or maturation of the disease, multiple biopsies should be performed periodically. That was not justified ethically. Therefore, to capture disease progression or maturation, we substituted multiple histologic studies for each biopsy that had been performed.

According to the INPC, ganglioneuroma is a tumor in the final stage of maturation. Because the process of tumor maturation requires time, ganglioneuroma is seen rarely in infants. In our series, none of the 45 neuroblastomas in group A were mature, but all tumors resected in patients greater than 24 months of age in group B were maturing ganglioneuroma (Fig 1). This suggests that immature neuroblastoma transforms into mature neuroblastoma after a period of approximately 18 months. Maturation of neuroblastoma is characterized histopathologically by a constellation of maturing ganglion cells. In our patient population, all neuroblastomas resected in patients aged 10 months or older had maturing ganglion cells (Fig 2), suggesting that the maturation process of mass-screened neuroblastomas begins at about 10 to 12 months of age.

The cellularity of a tumor is associated with its mitotic activity, which is indicated by mitosis karyorrhexis index (MKI). A high MKI is correlated with adverse clinical and biologic manifestations. In our series, moderate to high values of MKI were seen in patients of age less than 10 months (Fig 3). Patients greater than 12 months of age had low MKI values, indicating that mitotic activity of neuroblastomas decreases around 12 months of age.

At our medical center, the cut-off value for urinary VMA and HVA in mass-screened patients has been 17.0 and 30.5 μg/mg creatinine, respectively. Although the levels of VMA in 4 group B cases returned to normal range at 20 months of age, the levels of HVA in all cases were within normal range at 24 months of age (Figs 4 and 5). Biochemical activity of the neuroblastoma produces catecholamines. Thus, a decrease in urinary VMA and HVA levels indicates that the number of biologically active tumor cells begins to decrease around 24 months of age.

In our 16 years of experience, 141 neuroblastomas have been detected by mass screening at the age of 6 months. Almost half of these originated from the adrenal gland. The experience leads to speculation that mass-screening–detected, localized adrenal neuroblastomas start to mature around 10 to 12 months of age. By about 24 months of age, the neuroblastoma has completed its biologic and histologic maturation and starts transforming to ganglioneuroma. Localized adrenal neuroblastoma detected by mass screening should be observed untreated, unless the tumor transforms into progressive disease. A gradual increase in size of the localized adrenal tumor does not require surgical removal.

REFERENCES