The prevalence of pineal cyst in patients with cerebral palsy

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PURPOSE
Pineal cysts are common incidental findings during magnetic resonance imaging (MRI) examinations. The etiology of pineal cyst development is still unclear. We aimed to determine whether there is an association between periventricular leukomalacia and pineal cyst prevalence.

METHODS
Clinical and MRI data of 201 patients with periventricular leukomalacia (110 female, 91 male; mean age, 6 years; range, 2–18 years) and 687 control patients (355 female, 332 male; mean age, 6 years, range, 2–18 years) who did not have any evidence of periventricular leukomalacia were independently evaluated by two radiologists for presence or absence of pineal cyst.

RESULTS
Pineal cysts were detected in 32.3% of the study group (65/201) and 8.4% of the control group (58/687) (P < 0.001). Patients with periventricular leukomalacia were more likely to have a pineal cyst. In terms of pineal cyst detection on MRI, interobserver reliability was high between the two radiologists.

CONCLUSION
The prevalence of pineal cysts is higher in patients with periventricular leukomalacia. We suggest that an ischemic process may have a role in the etiopathogenesis of pineal cyst development.

Methods
This retrospective study was approved by the Ethics Committee of our institute. The study coordinator, with five years’ experience in neuroradiology, reevaluated MRI data of 250 patients who had been treated and/or followed up with the diagnosis of cerebral palsy (CP) between January 2010 and January 2014, from the picture archiving and communicating system of our hospital. The diagnosis of CP is established clinically through the identification of symptoms and signs regarding impaired cognitive development and motor impairment of cerebral origin. Forty-nine patients with CP were excluded. The exclusion criteria were existence of deep grey matter and/or cerebellum abnormalities, brain malformation, normal brain MRI and unavailability of clinical data. Thus, 201 patients with CP and PVL on MRI were included in the study constituting the study group. Of patients, 140 (69.6%) were diagnosed as spastic type CP, while 61 (30.4%) were dyskinetic type CP. All patients had volume loss in the white matter at centrum semiovale and/or periventricular region and/or increase of signal intensity in periven-
Pineal cysts were detected in 32.3% of patients with PVL. Among those patients, 687 (53%) did not have any brain abnormality on MRI and were included in the control group. The study coordinator matched control (n=687) and study (n=201) groups and presented them to two experienced radiologist as a randomized excel file.

Two radiologists having 12 and 7 years of experience in neuroradiology, respectively, evaluated the images of 888 patients independently and noted the existence of pineal cyst, if any, and the maximum dimension and properties of the pineal cysts. Radiologists were blind to the purpose of the study. They only evaluated the pineal gland and did not assess the other parts of the brain. Study coordinator did not contribute to the evaluation of the images. All images were obtained with a 1.5 Tesla MRI device (Achieva, Philips Healthcare). The standardized MRI protocol consisted of 5 mm sagittal and coronal T1-weighted spin echo slices (TR, 400 ms; TE, 115 ms; matrix size, 512×512), and 5 mm axial T2-weighted fast spin echo slices (TR, 5040 ms; TE, 115 ms; matrix size, 512×512). Contrast-enhanced sequences were obtained in 36 of 201 patients in the study group and 199 of 687 patients in the control group.

Statistical analysis

All statistical analyses were achieved using a commercially available software package (SPSS version 16.0, SPSS Inc.). Pearson’s chi-square test was used for categorical variables. A P value < 0.05 was considered statistically significant. Logistic regression analysis was performed to determine whether age and sex predicted the odds of pineal cyst existence. Kolmogorov-Smirnov test was used to detect normal distribution of variables. Mann-Whitney U test was used to determine any age differences between the patient and control groups.

Interobserver reliability ratios were expressed with Cohen’s kappa (κ) coefficient, where a value of 1 shows complete agreement and 0 shows no agreement or agreement by a chance (7). κ values were interpreted as follows: <0.20, slight agreement; 0.21–0.40, fair agreement, 0.41–0.60, moderate agreement, 0.61–0.80, substantial agreement, and 0.81–1.00, almost perfect agreement (8).

Results

The study group included 110 females (54.7%) and 91 males (45.3%), with a median age of six years. Among 201 patients with CP, 189 (94.03%) had preterm labor history (<37 weeks), while 12 patients (5.97%) were born at term. Mean gestational age was 30.8±3.7 weeks and mean birth weight was 2150±290 g. Control group included 355 females (51.7%) and 332 males (48.3%), with a median age of six years. Among control patients, 143 were preterm, 64 were post-term, and the remaining 480 subjects were born at term. For the control group, mean gestational age was 38.41±5.53 weeks and mean birth weight was 3190±580 g. Demographic findings of both study and control groups are given in Table 1.

Pineal cysts were detected in 32.3% of the study group compared with only 8.44% of the control group (P<0.001). The dimensions of pineal cysts were not normally distributed. The maximum diameter of pineal cysts ranged 1.3–11 mm in patients with PVL (median, 6.0 mm) and 2.1–30 mm in control subjects (median, 8.0 mm) (Fig. 1).

All pineal cysts were hypointense on T1-weighted images, hyperintense on T2-weighted sequences, and also isointense or slightly hyperintense on fluid attenuated inversion recovery (FLAIR) sequences. In contrast-enhanced sequences of 439 patients, none of the cystic lesions enhanced with contrast material (Figs. 2 and 3). Logistic regression analysis showed that the age distribution of subjects with PVL did not differ from those without PVL (P = 0.440). The sex distribution of those with PVL likewise did not differ from that of the total sample (P = 0.779) (Table 2). There was no difference between the patient and control groups in terms of age (P = 0.298). There was good reliability between the two observers for the existence of pineal cysts (κ=0.89, P < 0.001).

Discussion

Our study shows that the prevalence of pineal cysts is increased in patients with PVL and CP. Pineal cysts were detected in 32.3% of patients with PVL and CP compared with only 8.4% of patients who did not have any brain abnormality on MRI.

Pineal cysts are the most common benign lesions of pineal gland and are usually detected incidentally at routine MRI examinations. There are some hypotheses about the development of pineal cysts. Some authors suggested that pineal cyst development is a physiologic...
maturation that may progress secondary to degenerative process, while others proposed that pineal cysts could occur due to necrosis or cavitation change following ischemic degeneration of intrapineal glial plate (2, 5). Bregant et al. (6) demonstrated a possible association between the pineal cyst and thinner corpus callosum in 14 patients with hypoxic ischemic encephalopathy. They proposed that the pineal cyst could be a benign consequence of mild hypoxia (6). Similarly, our results showed that the prevalence of pineal cysts was higher in patients with PVL and CP when compared with the patients who did not have any brain abnormality on MRI.

Hypoxia and ischemia, which are predisposing factors for development of PVL, can also lead to cyst development inside the pineal gland. PVL is an ischemic reperfusion injury of white matter that causes pre-oligodendrocyte destruction and myelination deterioration, with contributory factors including hypotension, hypocarbia, and infection (9, 10). Oligodendrocyte precursors are susceptible to free radicals and exotoxicity induced by hypoxic ischemic injury. Pinealocytes may also be vulnerable to free radicals and toxins induced by hypoxia and ischemia.

In preterm neonates, mild-to-moderate hypotension may affect the white matter which is seen as hyperintense signal changes on T2-weighted images, periventricular cyst formation, and PVL. At the end-stage, it is characterized by ventriculomegaly with irregular borders, loss of white matter volume, and thinning of corpus callosum (10). In our study we just detected the end-stage findings of PVL since we did not have the MRI findings of study and control patients shortly after the birth.

The term of PVL was first established by Banker and Larroche in 1962 (10). They described a series of histological changes in the white matter of preterm infants. Although PVL is associated with preterm labor, it might be seen in term infants, as well (10). There were 12 patients (5.97%) with CP who were born at term, in our study. In term infants, PVL is related with perinatal hypoxia, complex cardiac disorders, extracorporeal membrane oxygenation, and chromosome abnormalities (11, 12). PVL is also the most common cause of CP in preterm infants (13). Abnormal MRI was observed in 88% of children with CP, and the vast majority of these abnormalities were

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**Figure 1.** a–f. Pineal cyst in a 3-year-old girl who did not have any findings or clinical data indicating periventricular leukomalacia. Axial T1-weighted image (a) shows a hypointense pineal cyst measuring 30 mm in diameter (arrow). Axial T2-weighted image (b) reveals hyperintense pineal cyst (arrow). Fluid attenuated inversion recovery (FLAIR) (c), coronal T2-weighted (d), and sagittal T1-weighted (e) images show that the pineal cyst is isointense with cerebrospinal fluid (arrows). Contrast-enhanced T1-weighted sequence (f) shows rim-like contrast enhancement along the cyst wall (arrow).
white matter abnormalities including increase in intensity on T2-weighted sequences, volume loss, and irregular dilatation of lateral ventricles (14).

Children with CP may have many signs and symptoms including motor dysfunction, intellectual impairment, visual and hearing loss, feeding problems, respiratory infections, and epilepsy. In these patients the role of cranial MRI is to establish the relationship between the lesion topography and motor type, and between lesion extension and functional severity (15). It is also surprising that pubertal development begins earlier in children with CP than normal population. Pineal gland has an important role in pubertal development and pineal cysts are reported to be related with precocious puberty (3, 16). Although the mechanism of precocious puberty in patients with CP is not clear, there could be a relationship between pineal cyst, CP, and precocious puberty.

Due to the use of three-dimensional (3D) gradient-echo sequences which allow acquisition of very high-contrast resolution images, the number of diagnosed pineal cysts increased significantly (5). There are various published reports about pineal cyst prevalence in the literature, but the results are inconsistent. This is not surprising since the detection of pineal cysts is related to magnetic field strength and technical parameters including slice thickness and sequences. For instance, in some studies which used two-dimensional sequences with ≥3 mm slice thickness, the prevalence of pineal cyst was reported as 0.14%–4.3%, while in the other studies that used 3D sequences with 1 mm isotropic voxel size or less, the prevalence was increased (17). Furthermore, Whitehead et al. (2) indicated the pineal cyst prevalence as 57% with volumetric 3D sequences at 3.0 T MRI device and Bump et al. (18) also reported the prevalence of pineal cysts to be 57.4% in children with the high-resolution 3D sequence of true fast imaging with steady state precession (true FISP). Furthermore, pineal cyst prevalence was higher in live children compared with the autopsy series in which the prevalence was reported to be 20%–40% (19, 20). In addition, 45% of those pineal cysts were
less than 2 mm. Thus, we can predict that more numerous and smaller cysts can be detected using MRI with thinner slices and higher resolution. In our study the prevalence of pineal cyst was 8.4% in the control group. This lower value could be related to the technical parameters and the slice thickness that we used.

Pineal cysts are generally hypo/isointense or hyperintense on T1-weighted and FLAIR images and iso- to hyperintense on T2-weighted images (3). However, signal intensity may change due to the content of pineal cysts. We did not encounter any complicated pineal cysts with hemorrhage or calcification in our study.

We had some limitations in this study. First, this was a retrospective study. Thus, we included patients who had routine cranial MRI examination. The slice thickness was 5 mm and pineal gland was not centered. In our study the prevalence of pineal cysts was lower than the other studies performed with 3.0 T MRI device or volumetric 3D sequences. Second, we could not obtain contrast-enhanced sequences in all of our patients with pineal cyst, since contrast administration is not needed to evaluate PVL. Thus, we considered pure cystic lesions that were isointense with cerebrospinal fluid as pineal cysts. However, patients with pineal cysts were followed for at least six months. We could not obtain volume measurements from both pineal cysts and corpus callosum due to our slice thickness. In addition, we did not conduct an interobserver reliability analysis between the size of pineal cyst and the age and sex of the patients. We did not compare the study and control groups in terms of the thickness of corpus callosum. Finally, we could not obtain data regarding the other predisposing factors of PVL development including perinatal asphyxia, cardiovascular disorders, chromosomal disorders or infection history.

In conclusion, we found that the prevalence of pineal cysts increased in patients with CP and PVL. Predisposing factors for PVL may have a role in the development of the pineal cysts as well. Although pineal cysts are mostly asymptomatic, they may cause various problems including pineal cyst apoplexy, precocious puberty, and headache; therefore, radiologists should be aware of them, and in case of CP evaluation, these insensible lesions should be reported together with white matter degeneration.

Conflict of interest disclosure
The authors declared no conflicts of interest.

References