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Magnetic resonance imaging based morphologic evaluation of the pineal gland for suspected pineoblastoma in retinoblastoma patients and age-matched controls☆

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ABSTRACT

Purpose: The purpose of this study was to evaluate the morphologic magnetic resonance imaging (MRI) characteristics of the pineal gland in retinoblastoma (Rb) patients without and with pineoblastoma in comparison to age-matched controls to improve early identification of pineoblastomas (trilateral retinoblastoma, TRb).
Methods and materials: 80 patients with retinoblastoma and 80 age-matched controls who had undergone brain MRI were included in this retrospective institutional review board approved cohort study. Two readers analyzed the following MR characteristics of the pineal gland: signal intensity on T1- and T2-weighted images, enhancement pattern, delineation of the gland, presence of cystic component, size of pineal gland and size of pineal cysts, respectively. A third reader assessed all images for the presence or absence of pineoblastoma.
Results: 3 patients were positive (TRb cohort) and 77 negative for pineoblastoma (non-TRb cohort). The mean maximum diameter of the pineal gland was 6.4 mm in Rb patients and 6.3 mm in age-matched controls. The mean volume of the pineal gland in Rb patients was 93.1 mm^3 and was 87.6 mm^3 in age-matched controls. Considering all available MRI scans the mean maximum diameter of the pineal gland in TRb patients was 11.2 mm and the mean volume in TRb patients was 453.3 mm^3. The third reader identified pineoblastomas with a sensitivity of 100% (3 of 3) and a specificity of 94% (72 of 77).
Conclusion: Our non-TRb patients did not show significant differences in the size of the pineal gland and pineal gland cysts compared to age-matched controls. The presented data can serve as a reference for the volume of normal pineal glands and pineal cysts in the diagnostic work-up of Rb patients with suspected pineoblastoma.

1. Introduction

Retinoblastoma (Rb) is a rare malignant disease of the developing retina with an incidence of 3% of children under 15 years and 9.5% of children under 4 years. However, Rb is one of the most common primary malignant intraocular tumors in childhood, comprising 4% of all malignant diseases in infancy [1]. Rb affects both eyes in about one third of cases at a median age of diagnosis of one year [2]. Unilateral disease is typically diagnosed later, at a median age of around two years. Bilaterally as well as a minority of unilaterally affected patients carry a constitutional mutation of the retinoblastoma gene. These hereditary Rb cases (about 45% of all cases) may develop a primitive neuroectodermal tumor (PNET) of the intracranial midline, mainly, the pineal gland. The term 'Trilateral Retinoblastoma' (TRb) describes the presentation of bilateral retinoblastomas together with the existence of a PNET within the pineal gland or the suprasellar space [3–5]. The reported incidence of PNET in Rb patients is 2–5% [6,7], of those the majorities are bilateral cases, but heriditary unilateral cases have been reported as well [8]. De Jong et al. reported in a meta-analysis of 23 retinoblastoma cohorts from 26 studies that the chance of pineal trilateral retinoblastoma is 4.2% (95% CI: 2.6–6.2%) in bilateral cases and the chance of non-pineal trilateral retinoblastoma is 0.8% (95% CI: 0.4–1.3%) [9].The WHO classifies pineoblastoma as a grade 4 tumor in the central nervous system that features a tendency to infiltrative growth and leptomeningeal tumor spread [10]. On magnetic resonance imaging (MRI) pineoblastoma presents as a mass lesion with intense signal enhancement of the solid tumor components after contrast application [4,11]. MR screening is recommended in all newly diagnosed Rb patients to detect TRb at a subclinical stage to optimize therapy [12,13].

Pineal cysts have been described in children with hereditary bilateral Rb, assuming that there may be a benign variant of TRb [11]. However, the presentation of a pineoblastoma may be partially or totally cystic in the majority of cases [4,14]. Therefore, evaluation of MR imaging

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characteristics of the pineal gland may be challenging in high-risk Rb patients, especially if the pineal gland is enlarged or of cystic appearance. Currently, there are no guidelines defining a suspicious pineal gland nor suggesting a follow-up scheme for suspicious pineal glands. In general, there is limited knowledge of the significance of minor radiomorphologic changes of the pineal gland of patients with Rb. It is therefore a challenge for the radiologist to rule out a pineoblastoma with a high level of confidence. To our knowledge, data of MR characteristics of pineal glands of Rb patients has never been compared to an age-matched control group.

The purpose of this study is to systematically evaluate the MR imaging findings of the normal pineal gland and of pineoblastoma in a large cohort of Rb patients in comparison to age-matched controls. Secondary, the diagnostic accuracy for identifying TRb in an Rb cohort is investigated.

2. Material and methods

2.1. Subjects

This retrospective analysis included Rb patients treated at our hospital between 1997 and 2013 and who had MR imaging of the brain. The diagnosis of retinoblastoma was confirmed by extensive ophthalmoscopy and MR imaging. The ethical board and the data security board approved this study. In total, 91 eligible patients were identified in the radiology data base with the key words “retinoblastoma” or “pineoblastoma” who had undergone baseline MRI of the brain. 5 patients had to be excluded due to untraceable MRI or insufficient image quality, and 6 patients were excluded because the final diagnosis was not Rb. The final cohort includes 80 patients with sufficient MR imaging, out of which 3 are positive (TRb cohort) and 77 negative (non-TRb cohort) for pineoblastoma. In addition, an aged matched control group of 80 patients has been collected, who had undergone MR imaging of the brain for various reasons and who had no pathology of the diencephalon.

2.2. Diagnosis

The gold standard for the diagnosis of pineoblastoma was the clinically established diagnosis based on the clinical patient chart. Clinical records were reviewed for family history of Rb, tumor laterality, time interval from Rb diagnosis to last follow-up and treatment. The attending ophthalmologist was contacted for further information about the last follow-up, potential death and treatment of all children. In order to achieve the most current follow-up of the retinoblastoma cohort we have been sending 77 questionnaires (reply rate of 42%, TRb patients have been excluded from any approach via mail) besides contacting the referring ophthalmologist and reviewing the patient charts.

2.3. MR imaging

MR imaging was performed on several different 1.0 and 1.5 Tesla scanners (Siemens Magnetom Vision, Symphony, Avanto or Aera, Philips Gyroscan Intera or 1.5 Tesla General Electric Genesis Signa) on three different hospital sites during the 17 year study period. Hence, MR imaging protocols of the brain varied and a minimum sequence protocol requirement was defined for inclusion of patients into the study cohort: either MR images covering the pineal gland in 2 dimensions or in 1 dimension with the pineal gland clearly visualized; a matrix size of 192 or above and a field-of-view of 220 mm or less, resulting in a minimal in-plane resolution of 1.15 × 1.15 mm. The vast majority of MR scans included at least 1 plane covering the pineal gland with a slice thickness of ≤3 mm.

2.4. MR image analysis

The 80 subjects included in the Rb cohort (TRb and non-TRb cohorts) had a total of 159 brain MRIs. Two independent readers with 7 and 12 years of experience in brain MRI, who were blinded to any clinical data, reviewed the 159 brain MRIs and the 80 brain MRIs of the control group with regard to the radiomorphologic appearance of the pineal gland. The following parameters were assessed: signal intensity on T1-weighted and T2-weighted images compared to gray matter, enhancement pattern after i.v. contrast application (homogeneous vs. heterogeneous), delineation of the gland (regular vs. irregular), texture of the gland (solid, partial cystic, cystic), size of the pineal gland in three dimensions (in mm) and size of a pineal cyst in the largest dimension, if present (in mm). Also, the volume (V) of the pineal gland was calculated according to the ellipsoid formula: $V = 4/3 * \pi * ap/2 * ml/2 * cc/2$. Disagreement in assessments of the texture of the gland at baseline MRI was resolved by a consensus reading session to be able to demonstrate differences between the groups TRb, bilateral Rb, unilateral Rb and the age-matched control group.

A 3rd radiologist (neuroradiologist with 9 years of brain MRI experience), who was blinded to the diagnosis of pineoblastoma, reviewed the 159 brain MRIs of the Rb cohort for the presence or absence of pineoblastoma (diagnostic accuracy study part, compliant with the STARD criteria [15]). Due to the rare incidence of TRb a prior training session was performed where the reader was shown various external MR images of a normal pineal gland and typical images of pineoblastomas derived from the literature. After this training session, the 3rd reader evaluated the MR images of the Rb cohort regarding the following question on a three-point Likert scale: does this MR study show a pineoblastoma (yes, unclear, no).

The sensitivity and specificity were calculated on a ‘patient level’ which means that a patient was correctly diagnosed as having a pineoblastoma if the pineoblastoma was diagnosed on at least 1 out of all available MRIs and on an ‘MR imaging level’ considering all available MRIs of all patients.

2.5. Statistical analysis

A comparison of the size of the pineal gland (pineal cyst, respectively) between the non-TRb group and the control group was performed using the Mann–Whitney U test. To compare the number of patients with pineal gland cysts the Chi^2-test was used. Differences between cystic

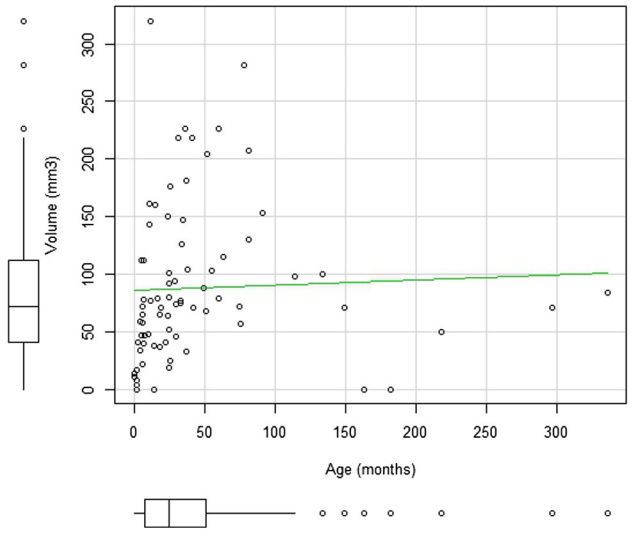

Fig. 1. Volume of the pineal gland in Rb patients. This graph illustrates the volume of the pineal gland in mm^3 (y-axis) of Rb patients plotted against age in months (x-axis). In 4 patients only 2 dimensions were available and the volume could not be calculated, these patients were not plotted onto the graph.