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Kystes de la glande pinéale dans le rétinoblastome: quel lien avec la maladie et les traitements?

Cysts of pineal gland in retinoblastoma: what link with disease and treatments?

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Cyst of the pineal gland in retinoblastoma: what link with disease and treatments

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ABSTRACT

OBJECTIVES. Retinoblastoma (Rb) represents the most frequent intraocular paediatric tumor, with an average incidence of 1:14'000 to 1:34'000 births. In 2006 we were first to report on pineal cysts that appeared to be more common in children with hereditary bilateral Rb. The aim of our study was to review in a larger patient cohort the occurrence of pineal cysts and to study the link with disease characteristics and treatments received.
METHODS AND PATIENTS. Observational retrospective study of clinical and radiological data of 103 patients treated for Rb who had undergone a cerebral magnetic resonance imaging (MRI) between 2006 and 2013 and had a follow-up. Clinical records were reviewed for sex, age at diagnosis, hereditary pattern of disease, tumor laterality, stage according to the International Classification of Retinoblastoma, age at first MRI, treatments received, date of first and last treatment and last follow-up, response to treatment, long-term outcome, time interval from diagnosis of Rb to the diagnosis of a pineal cyst, and genetic data if known. Radiological reports and brain images were reviewed for each patient with pineal cyst to record its size and change over time.
RESULTS. Of 103 patients with Rb 56 had unilateral and 47 bilateral disease. Ninety-five were sporadic Rb while 8 were familial. Forty-nine MRIs out of 103 (47.6%) presented a pineal cyst and were reviewed by a neuroradiologist to verify aspect and the size of the pineal gland. Occurrence of cysts was more frequent in bilateral disease, sporadic disease, in presence of a documented genetic mutation and in group D or E, but without statistically significance. No impact of treatment on the occurrence of cysts could be demonstrated. At 1 year of follow-up, cysts had higher growth in bilateral Rb and those with documented genetic mutation, but without statistical significance. None of the other parameters showed significant impact on growth.
CONCLUSIONS. We found a high incidence of pineal cysts in Rb patients, but could not demonstrate a significant relationship to the hereditary subgroup or genetic mutation. The evolution was benign without malignant transformation in absence of atypical radiological signs. The higher incidence however compared to a healthy paediatric population clearly indicates that pineal cysts are part of the disease-related midline brain abnormalities.

Key words: retinoblastoma, pineal cyst,

INTRODUCTION

Retinoblastoma (Rb) is a rare disease but represents the most frequent intraocular paediatric tumor, with an average incidence of 1:14'000 to 1:34'000 births[1-4]. It can occur as unilateral or bilateral disease. Bilateral Rb is always hereditary and is caused by a mutation of the RB1 gene. This gene is also responsible for other related abnormalities, such as malignant tumors of the pineal gland or other cancers[5].

Trilateral retinoblastoma (TRb) is a well-known entity constituted by a unilateral or bilateral Rb alongside with an intracranial midline primitive neuroectodermal tumor (PNET), which appears more frequently in the pineal gland[6-9]. These tumors are most often malignant pinealoblastomas. In 2006 we were first to report on pineal cysts that appeared to be more common in children with hereditary bilateral Rb[10,11] compared to the healthy paediatric population[12] (5.3% vs 1.8%) suggesting the possibility of a new entity, a benign variant of trilateral Rb that may be linked to the mutation, or to treatment-induced modifications (systemic chemotherapy, external beam radiotherapy). Since then various authors have observed the occurrence of benign pineal cysts in this patient population[13-15]. Along with considerable advances in the treatment of Rb in the field of conservative treatment modalities allowing a higher eye preservation rate without systemic chemotherapy and avoidance of radiotherapy, technological advances in MRI imaging have been obtained which allow a more precise visualization of the ocular and intracerebral structures and thus a better distinction between a begin cyst or a tumor of the pineal gland[16].

Patients with Rb have a risk of less than 0.5% to develop a TRb in sporadic unilateral disease, of 5-13% in sporadic bilateral disease and of 5-15% in familial bilateral Rb[6]. While Rb is in most cases curable[17], TRb remains an often fatal high risk disease.¨ Early detection provides a better chance of survival[18]. However, the usefulness of systematic MRI follow-up is still debated[19]. Less is known on the natural behaviour of benign pineal cysts. Since we kept the same imaging approach for our patients over the last 10 years, we decided to review the radiological behaviour of pineal cysts and to look for relationships to various clinical factors.

METHODS

This is an observational retrospective study of clinical and radiological data of 103 patients treated for Rb who had undergone a cerebral magnetic resonance imaging between 2006 and 2013 and had a clinical and radiological follow-up (FU). MRI was performed in every patient at diagnosis. Patients with bilateral Rb had an annual follow-up until the age of six years for early detection of tumors of the pineal gland. Patients with unilateral disease were not followed by MRI if the initial imaging revealed no abnormality, being less at risk to develop a pinealoblastoma. Whenever a pineal cyst was identified, imaging was repeated every 3-6 months until non-progression or absence of modification was secured (last MRI at FU). Cyst growth was evaluated based on first MRI, MRI at 1 year of FU and last MRI at FU.

Clinical records were reviewed for sex, age at diagnosis, the hereditary pattern (sporadic vs familial) of disease, tumor laterality (unilateral, bilateral), stage according to the International Classification of Retinoblastoma, date of first MR imaging, treatments received (systemic chemotherapy, local treatments, external beam radiotherapy), date of first and last treatment, and last follow-up, response to treatment (stable, favourable, unfavourable), long-term outcome (cure, death), time interval from diagnosis of Rb to the diagnosis of a pineal cyst diagnosis, and genetic data if known.

Radiological reports were reviewed for each patient to record the aspect of the pineal gland. All patients had undergone the same MRI protocol: 3T MRI with sagittal or transverse unenhanced T1-weighted images or T2-weighted images and post-contrast T1- weighted images. For those who had a pineal cyst described on the report, brain images were reviewed by the neuroradiologist involved in The European Retinoblastoma Imaging Collaboration (ERIC) group[16]. The pineal gland was measured in two planes and volume was calculated. The presence of a pineal cyst was classified according to the Classification of Pineal cysts in children under 5 years from the University Hospital of Essen made by the ERIC project (unpublished).

STATISTICS

The statistics analysis was done by a statistician from the Institute of Social and Preventive Medicine. The link between the presence or absence of cysts and the various items was tested by the Pearson's chi-squared test if all the cells of the table had a frequency of 5 patients minimum. If there were four or less patients in one category the Fisher's exact test was used.

The link between the presence of cysts and age at diagnosis of Rb was tested by comparing the age of patients with cysts to those without cysts using the Mann-Whitney test.

Cyst size at the defined time points was compared, with the Mann Whitney test for groups for binary variables and with the Kruskal-Wallis test for groups that contained three or more categories in order to evaluate size growth over time. The link between age and cyst growth was estimated by the tau de Kendal correlation coefficient.

We considered a significance threshold of alpha = 0.05.

The risk of developing a pineal cyst (Table 2) was analysed using a logistic regression analysis. Groups were dichotomised (A-C vs D-E) to minimize the number of categories. The odds-ratio represents an estimation of the risk of having cysts for patients with Rb compared to a control group. OR>1 means that the risk is higher than the one of control group. OR<1 means that the risk is lower than the one of control group. For age, OR represents the risk for a patient with a certain age compared to a patient who is one year younger. The risk of the estimated value is higher (if OR>1) or lower (if OR<1) for each additional year of age.

RESULTS

Patient characteristics (Table 1):
There were 103 patients eligible for our study, 47 boys and 56 girls. Their mean age at diagnosis was 1.6 years. Of 103 patients with Rb, 56 had unilateral and 47 had bilateral disease, for a total of 113 eyes with the following distribution by disease Group: Group A 4, Group B 20, Group C 13, Group D 54, Group E 22 eyes. Ninety-five cases were sporadic and 8 were familial. Sixty-two out of 103 patients had available genetic results with RB1 mutation in 38/62 (62%). All patients had an MRI performed at diagnosis. Forty-nine out of 103 MRIs (47.6%) presented a pineal cyst and were reviewed by the neuroradiologist for size verification.

Follow up:
All patients had an ophthalmological FU at a defined time schedule according to their disease status and treatment, to secure cure and long-term FU. Analysis of the evolution of the cyst was possible in 43/49 cases with pineal cyst. Five out of 103 patients died (4.9%). The first patient had a sporadic unilateral Rb treated with systemic chemotherapy. An MRI was performed for intraocular relapse, which revealed an asymptomatic pinealoblastoma of 2 x 2.5 cm. The child died from toxicity of high dose chemotherapy. Three other patients died from a progressive disease: 2 presented an invasion of the central nervous system at diagnosis, and in 1 the parents refused enucleation after failure of conservative treatments. The fifth patient presented a sporadic bilateral Rb and was diagnosed with an atypical pineal cyst. A close MRI follow-up was recommended, but not performed. Nine months later the MRI revealed a pinealoblastoma, which responded only partially to intensive treatment and finally progressed.

Pineal cysts (Table 2):
The occurrence of pineal cysts was more frequent in bilateral Rb but without statistical significance compared to unilateral disease (chi squared test, p=0.296). Mean age at diagnosis of Rb for patients with cysts was 1.3 years and in those without cysts 1.9 years, which was not statistically significant (Mann Whitney test, p=0.184). The percentage of patients with cysts was higher when Rb was sporadic than familial (48.42% vs 37.50%), and in presence of a genetic mutation (55.26% vs 33.33%), but without statistical significance. Although cysts were more common in more advanced disease stage such as Group D and E Rb, there was no difference to the less advanced disease groups A-C; for both disease group categories the risk to develop a cyst was equal with OR being 1.

Treatments:
The presence of cysts was not correlated to any treatment received (systemic chemotherapy, local treatments, radiotherapy), alone or combined. (Fisher's exact, p = 0.916).

Cyst growth (Table 3):
At one year since first MRI, the cysts showed a mean and median growth of 1.5 mm each in unilateral Rb. In bilateral Rb, there was a mean growth of 18.4 mm and

median growth of 12 mm. The difference was statistically not significant. (Mann-Whitney test, p=0.089).
Cyst growth was also correlated to eye laterality, age at diagnosis of Rb, sporadic or familiar occurrence of Rb and genetic data. Only the latter seem to have had an impact on growth, as in presence of demonstrated genetic mutation the cysts showed a mean growth of 21.8 mm and median growth of 8.9 mm compared to those without genetic mutation, which on the contrary even showed a decreased mean growth of -3.7 mm and median growth of -5.4 mm, without however reaching significance compared to absence of genetic mutation (Mann-Whitney test, p = 0.0682).
We also looked at cyst growth at the last follow-up MRI (Table 4). When correlated to the same parameters such as unilateral vs bilateral Rb, age at diagnosis of Rb, sporadic vs familiar Rb, presence or absence of genetic mutation, none had a significant impact on growth.

DISCUSSION

This study describes a large cohort of Rb patients and reviews the occurrence of pineal gland cysts. The latter have increasingly been described for the past ten years and are part of the clinical picture observed in Rb patients. In our retrospective study, we found an incidence of pineal cysts of 47.6% on the baseline MRI performed at diagnosis of Rb. This is much higher than what has been described by other groups. Rodjan and al.[9] reported a total incidence of pineal cysts of 5.4% and an incidence in the hereditary subgroup of 2.2%, which compares well with the incidence in a healthy paediatric population younger than five years of age which has an equivalent age frame as the Rb population[20]. An explanation for this higher incidence in our patient cohort could be technical. High sensitivity 3T MRIs allow a much earlier and more precise detection of cystic modifications of the pineal gland. Another reason for detecting more pineal cysts could be improved expertise of the neuroradiologists involved in an European Retinoblastoma Imaging Collaboration (ERIC) composed of neuroradiologists from 5 participating countries (among them our neuroradiologist) who are working on a standardized description and classification of pineal cysts in Rb patients.

As in our former study where we stated a higher incidence of pineal cysts in hereditary Rb[11], we found in this larger patient cohort again a higher incidence in patients with bilateral disease and in those who had a documented genetic mutation, which is line with Abramson et al.[14], but could not prove it statistically. On the contrary, we observed proportionally as many cysts in sporadic Rb as in familial cases (48.42% vs 37.50%). The extreme difference in numbers (95 sporadic vs 8 familial) might be a reason for statistical non-significance. Furthermore, 40% of lacking genetic information and our small sample size could have biased our evaluation. A bigger patient number with genetic results might reveal a relationship to the occurrence of cysts, as the Rb population is known for various midline brain abnormalities in contrast to a normal paediatric population[9] which could also include cysts as suggested earlier [10].

We looked at age at diagnosis of Rb and potential impact on developing cysts. No relationship could be found between age and presence of pineal cysts, as mean age at diagnosis of patients with cysts (1.3y) was not significantly different from those without cysts (1.9y). The occurrence of pineal cysts in the healthy paediatric population has been related to older age by several authors[12,21]. Whitehead and al.[21] retrospectively reviewed 3T MRIs of 100 healthy children aged from 1 month to 17 years. They found a prevalence of 57% with an equal distribution through the ages, with a mean age of occurrence of 6.6 years and median age of 6 years.

Although cysts were more common in more advanced disease stage such as group D or E Rb, there was no difference to the less advanced disease groups A-C. The risk to develop a cyst was the same as in a control group (OR 1).

Shields et al. compared in 2001 142 patients having received systemic chemotherapy as treatment to 72 patients treated without chemotherapy: during 47 months of follow-up, no intracranial neuroblastic tumor developed in the chemo reduction group[22]. We found no correlation either between the presence or absence of cysts and any kind of treatment the patients have received.

As indicated in Table 3 an interesting finding in our analysis was the evaluation of cyst growth at 1 year after its diagnosis. Growth was higher in bilateral Rb, and in presence of genetic mutation. On the contrary, those without genetic mutation even showed a decrease in growth. At last follow-up MRI none of all parameters analysed influenced significantly growth. Whether the presence of a genetic mutation plays a role in the promotion of faster cyst growth at the beginning of its development only, or whether treatment-related factors could on the contrary be responsible of stabilization or decrease on size of the cysts, remains open. Longer patient FU is needed with regard of the rapidly moving treatment modalities for patients with Rb.

According to Whitehead and al.[21], cysts showed a trend of growth with increasing age which was not signifcant. They used three measures for pineal volume calculations in contrast to us who used only two ; furthermore their cohort did not focus on Rb patients as ours. Several other studies in healthy children did not report either changes in cyst growth over time with at least 6 months of FU[11,13,14,23,24]. Mandera et al. described cyst stability of 96% (23/24)[25] over a mean follow up of 38 months. As in our hands, cysts have also been reported to decrease[14,21,23], or even resolve spontaneously[13].

Pineal cysts are benign and most of the time cause no symptoms[14,20,21,23,25]. Our study confirms that most of pineal cysts remain stable with time in children with Rb and are at low risk of progression. This speaks in favour of cysts as being benign entities. Only 1 patient presented an atypical pineal cyst at diagnosis of Rb with a cystic and solid part. In spite of the given recommendation to follow-up closely the cyst by MRI, the examination was repeated only 6 months later and revealed a malignant pineal tumor, which progressed after initial response to chemotherapy, with fatal outcome.

Literature reports variably on cysts and gender. Whitehead et al. observed cysts more frequently in girls than in boys, with a prevalence of 67% vs 57%[21]. Others found no gender predominance[14]. In our study we did not analyse this parameter that didn't seem relevant to us in the context of Rb.

The retrospective approach and incomplete data are the major limiting factors of our study not allowing confirming significance for some trends observed. In order to clarify the relationship of pineal cysts in Rb patients and their natural behaviour, further prospective studies are needed. Its high incidence however compared to a healthy paediatric population clearly indicates that pineal cysts are part of the disease-related midline brain abnormalities.

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Table 1. Patient characteristics

Variable	Categories	n (%)
Gender	Male	47 (46.6)
	Female	56 (54.4)
Family History	Negative (sporadic)	95 (92.2)
	Positive (familial)	8 (7.8)
Laterality	Unilateral	56 (54.4)
	Bilateral	47 (46.6)
Genetic	Genetic mutation	38 (36.9)
	No genetic mutation	24 (23.3)
	No genetic analysis	41 (39.8)
International classifcation	Group A	4 (2.67)
	Group B	20 (13.34)
	Group C	13 (8.67)
	Group D	54 (36)
	Group E	22 (14.67)
	No data	37 (24.67)
Pineal cyst	Presence	49 (47.6)
	Absence	54 (52.4)

Table 2. Pineal cysts and correlation to clinical characteristics

Variable	Category	n	with cysts (%)	no adjustment			adjustment to laterality		
				OR	IC à 95%	P	OR	IC à 95%	P
Laterality	unilat. (ref.)	56	24 (43)	1					
	bilat.	47	25 (53)	1.52	0.69-3.51	0.3			
Eye	bilateral (ref.)	47	25 (53)	1					
	left	27	11 (41)	0.60	0.23-1.57	0.3			
	right	29	13 (45)	0.61	0.28-1.81	0.48			
Age				0.86[1]	0.69-1.08	0.19	0.88[1]	0.69-1.11	0.286
Family history	negative (ref.)	95	46 (48)	1			1		
	positive	8	3 (37.5)	0.64	0.14-2.83	0.555	0.51	0.11-2.36	0.386
RB1 mutation	absent. (ref)	24	8 (33)	1			1		
	present	38	21 (55)	2.47	0.85-7.15	0.1	2.70	0.63-11.64	0.183
Left eye	D, E (ref)	37	18 (49)	1			1		
	A, B ou C	20	8 (40)	0.70	0.23-2.12	0.532	0.70	0.21-2.31	0.557
Right eye	D, E (ref)	43	23 (53)	1			1		
	A, B ou C	17	6 (35)	0.47	0.15-1.51	0.2	0.47	0.14-1.57	0.220

Table 3. Mean and median growth at one year MRI

	n	mean growth	sd	median growth	igr	min	max	p
Bilateral	14	18.39868	27.67028	12.0483	27.2906	-6.93	92.1788	0.0890
Unilateral	9	1.520611	11.50436	1.4841	18.3139	-14.6766	14.354	
Left eye	5	5.2912	8.97059	8.168	15.8364	-5.442	13.8226	0.1852
Right eye	4	-3.192625	13.86809	-6.22395	22.22335	-14.6766	14.354	
Sporadic	23	11.79422	23.90585	8.168	20.5193	-14.6766	92.1788	
Familial	0	-	-	-	-	-	-	-
Genetic mutation	13	14.44449	25.48145	8.9234	19.3723	-5.8341	92.1788	0.0682
No genetic mutation	5	-3.74878	11.85452	-5.442	15.4161	-14.6766	13.8226	

Table 4. Mean and median growth at last follow-up MRI

	n	Mean growth	sd	Median growth	igr	min	max	p
Bilateral	22	21.84826	33.89725	10.70295	29.0599	-8.0992	135.0666	0.1348
Unilateral	18	5.757278	10.83305	1.81355	18.0288	-11.7379	22.8824	
Left eye	10	6.81202	10.75394	5.46215	15.4626	-6.7596	22.8824	0.3156
Right eye	8	4.43885	11.52128	0.5087	19.5863	-11.7379	18.8795	
Sporadic	37	14.05162	26.74657	7.9348	20.267	-11.7379	135.0666	0.9795
Familial	3	21.4609	37.29516	7.5586	70.5967	-6.8863	63.7104	
Genetic mutation	19	18.11905	33.07184	7.9348	28.8279	-6.8863	135.0666	0.4451
No genetic mutation	6	6.496433	6.496433	1.62275	18.8126	-5.9773	22.764	