

# Baseline Central Nervous System Magnetic Resonance Imaging in Early Detection of Trilateral Retinoblastoma: Pitfalls in the Diagnosis of Pineal Gland Lesions

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**Abstract.** *Background:* Trilateral retinoblastoma (TRB) is a rare disease associating bilateral retinoblastoma (RB) with primitive intracranial neuroblastic tumor. *Aim:* To verify the occurrence of TRB in a single-Center case series and point out the clinical relevance of a baseline brain magnetic resonance imaging (MRI) in RB, focusing on pineal gland lesions. *Patients and Methods:* Baseline MRI was routinely performed in all cases of RB from 1999. All MRIs were reviewed for this study and the RB database was checked in order to identify patients characteristics, treatments and follow-up. *Results:* A total of 107 patients with RB were diagnosed between 1999 and 2012. Sixty-two patients had unilateral RB and 45 bilateral RB. MRI revealed the presence of pineal gland lesions in 10 patients (9%); seven were considered pineal benign cysts (6.5%), while in three patients (2.8%), TRB was suspected. All patients with TRB presented hereditary RB. In one patient, the suspected TRB was metachronous and in the other two patients was synchronous. Biopsy was not performed. Cerebrospinal fluid (CSF) was negative in all patients. The MRI modification, before treatment in the first case and later in the second case, confirmed the TRB diagnosis. The third patient died due to progressive Central Nervous System (CNS) disease that clearly confirmed the TRB diagnosis. None of the three patients had

received prior chemotherapeutic treatment. *Discussion:* TRB represents a rare condition in this series, occurring in three (2.8%) out of all patients with RB. A synchronous presentation with small lesion seems more frequent when a baseline MRI is performed. When a histologically-proven diagnosis is not available, a suspected diagnosis should be considered with caution and only follow-up will confirm the diagnosis. A wait-and-see approach should be considered.

Trilateral retinoblastoma (TRB) is a rare condition characterized by the occurrence of an intracranial neuroblastic tumor, usually in the pineal gland or in the supra/parasellar region, associated with bilateral or, less frequently, unilateral retinoblastoma (RB) (1-3). The risk of developing TRB, in familial RB or sporadic bilateral RB, has been reported to be 3-15%, while it is less than 0.5% in sporadic unilateral disease (1, 3-6). In most TRB cases, a chromosome 13q14 deletion has been reported (7-10). Moreover, children with familial *RBI* mutation seem to have a greater incidence of TRB than patients with *de novo* germline mutations (11-12).

TRB has a poor prognosis. Synchronous TRBs are more often asymptomatic and significantly smaller than metachronous TRBs (9). Magnetic resonance imaging (MRI) screening allows earlier TRB detection of still asymptomatic and small tumors (less than 15 mm), which are associated with a more favorable outcome. However, it is still controversial if screening improves prognosis and a large prospective trial is needed to solve this issue (13-15).

Recently, Rodjan *et al.* focused on clinical and MRI findings in a multicentric retrospective study (14). The authors confirmed the importance of baseline brain MRI for detecting TRB at a subclinical stage. Moreover, they suggested a possible over-estimation of the incidence of

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Table I. Patients' characteristics.

Patient	Gender	Age (months)	EI	Ocular stage	TRB presentation	Genetics	Family RB history	RB treatment
1	M	18	B	B/E	M*	<i>RBI</i> mutation	Yes	Enucleation and focal treatment
2	F	10	B	E/D	S	<i>RBI</i> mutation	No	None
3	F	16	B	E/D	S	13q14 deletion	No	None

EI, Eye involvement; RB, retinoblastoma; TRB, trilateral retinoblastoma; B, bilateral; ocular stage according to Linn Murphree (Reference 16), M, metachronous; S, synchronous. \*15 months after diagnosis.

metachronous TRB, because in the series presented, no baseline brain MRI had been performed.

The aim of the present study was to verify the occurrence of TRB in a single-center case series and to point out the clinical relevance of baseline brain MRI, routinely performed at the time of RB diagnosis or referral, in the detection of benign pineal gland lesion and TRB. Moreover, we speculate on how to consider a small synchronous pineal lesion suggestive of TRB, highlighting the importance of a multidisciplinary team in order to correctly address questions related to TRB diagnosis and treatment.

### Patients and Methods

The institutional RB database was reviewed to identify patients with RB diagnosed from January 1999, when in our Institution a baseline MRI started to be performed. All MRIs performed at diagnosis were reviewed as all follow-up MRIs for patients with a pineal gland lesion. The Institutional Review Board approved this retrospective study.

The medical records of patients with TRB were reviewed in order to identify clinical characteristics and gather a complete clinical history, including data concerning presentation, age, gender, family history of RB other malignancies, genetic and ocular stage. All patients were restaged according to Linn Murphree (16).

The brain MRI evaluation of the baseline RB protocol, included at least sagittal and axial T1-weighted images (T1WI), with/without contrast, or 3D T1WI with/without contrast, axial T2WI, diffusion-weighted images (DWI) with apparent diffusion coefficient (ADC) maps. Two experienced neuro-radiologists with more than 15 years' experience reviewed all MRI studies from patients with pineal gland lesions. The pineal region MRI findings were considered strongly suggestive for malignancy when one of the following findings was present: marked enlarged size of the gland, particularly when necrotic changes were present; irregular ring enhancement of its cystic wall; decrease in size; decreasing size after treatment; and changes of the MRI appearance of the gland after RB treatment.

### Results

Between January 1999 and December 2012, 107 patients with RB were diagnosed at the Bambino Gesù Children's Hospital; the male/female ratio was 58/49; the median age at diagnosis was 10 months (range=0.5-73 months). Sixty-two patients had unilateral and 45 bilateral RB.

MRI revealed the presence of pineal gland lesions in 10 patients (9.3%); seven were considered pineal cysts (6.5%), while in three patients (2.8%), a TRB was suspected according to the criteria above. The three patients were found to have asymptomatic TRB: this was metachronous in one patient and synchronous in the two remaining cases. TRB occurred in three out of 45 (6.7%) cases of bilateral RBs, while no patient with unilateral RB was found to have TRB. Moreover, TRB occurred in one out of 15 (6.7%) cases of familial RB. Age at diagnosis of these three patients was 18, 16 and 10 months, respectively. An *RBI* aberration was identified in all cases (see Table I for details) (17). None had previously received chemotherapeutic treatment; the patient with metachronous TRB had received focal treatment to the right eye and enucleation of the left eye at diagnosis (18). Examination of cerebrospinal fluid for metastatic disease was negative in all patients. All three cases were proposed and discussed for surgical approach with the neurosurgery team. Surgery of the three intracranial tumours, including biopsy, was not performed due to the small size of the lesions, without mass effect on adjacent structures or hydrocephalus.

### Case Reports

*Patient 1.* An 18-month-old child with bilateral RB was referred to our Institution for a pineal lesion detected on brain MRI screening 15 months after the initial diagnosis of RB. The patient had a circumscribed pineal mass presenting well-defined borders and a maximum diameter of about 15 mm. The lesion had a slightly inhomogeneous signal in both T1 and T2W images and exhibited homogenous enhancement on contrast MRI sequences (Figure 1). The MRI lesion progressed in volume from the initial MRI to the second MRI performed on admission to our Institution, supporting the TRB diagnosis. The patient was treated with conventional plus two courses of high-dose chemotherapy based on thiopeta, carboplatin and etoposide followed by peripheral blood stem cell rescue as previously reported (18) and is alive in complete remission more than 10 years from RB diagnosis.

*Patient 2.* A child 10 months old at the time of bilateral RB diagnosis presented a 7 mm oval, solid pineal gland (Figure

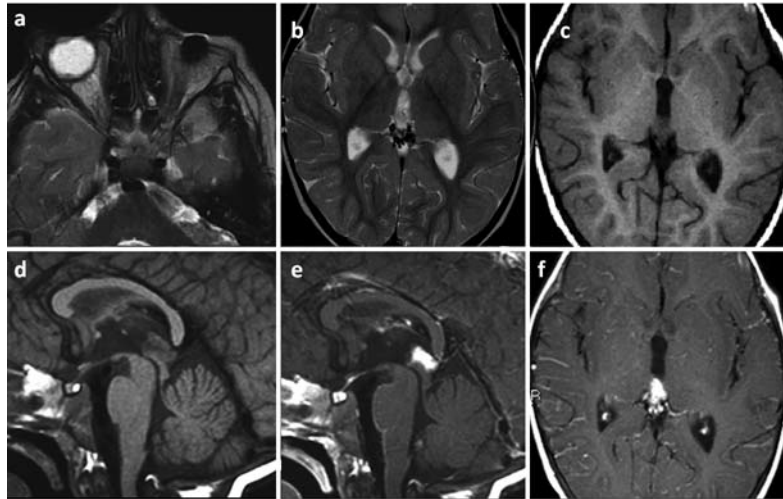


Figure 1. Patient 1. Axial T1-weighted images (T1WI) (a) show the enucleated left eye and a small in the right eye (arrow). Axial TSE T2WI (b), axial and sagittal T1WI (c, d) reveal a well-circumscribed pineal mass, with a maximum diameter of 15 mm. Sagittal (e) and axial (f) SE T1WI images with contrast show a homogeneously enhancing pineal mass.

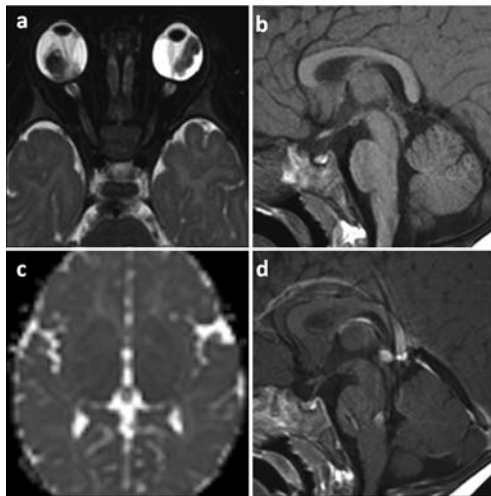


Figure 2. Patient 2 (first magnetic resonance imaging). Axial T2WI (a) shows a bilateral. Sagittal SE T1WI (b) presents a 7-mm solid pineal gland with low apparent diffusion coefficient (ADC) value (c). The pineal gland shows and intense and homogeneous contrast enhancement (d).

2). The gland showed low ADC value and intense and homogeneous contrast enhancement. The patient was treated with conventional chemotherapy (carboplatin plus etoposide followed by carboplatin/etoposide/ifosfamide), focal ophthalmic treatment and two courses of high-dose chemotherapy (busulphan/melphalan and thiotepa) followed by peripheral blood stem cell rescue. After chemotherapy, the lesion progressively shrank and evolved into a cystic appearance, showing an irregular enhancing ringed wall with

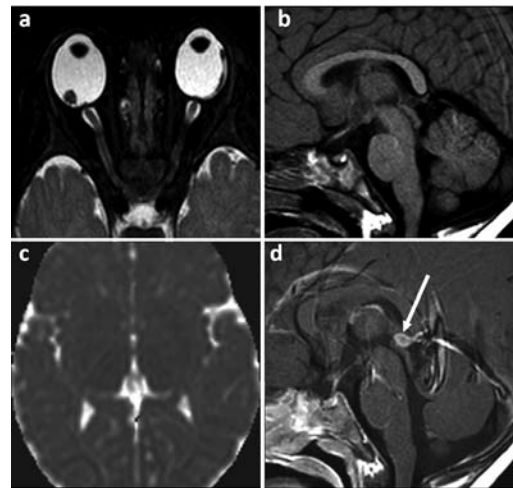


Figure 3. Patient 2 (second magnetic resonance imaging after six months). Axial TSE T2WI (a) shows a marked reduction in the size of the ocular mass, bilaterally. Sagittal SE T1WI (b) demonstrates the initial cystic evolution of the pineal gland mass, presenting a more heterogeneous signal, confirmed by the higher ADC values compared to the previous study (c). The sagittal T1WI post-contrast image (d) reveals the presence of an irregular enhancing ring wall with tiny nodules (arrow).

tiny nodules (Figures 3 and 4), supporting the neoplastic origin. The patient is alive with a surviving eye and without evidence of CNS disease at three years from diagnosis.

*Patient 3.* A 16-month-old child with bilateral RB showed a synchronous pineal lesion. The lesion measured 8 mm in diameter, presented an anterior small cystic component and a

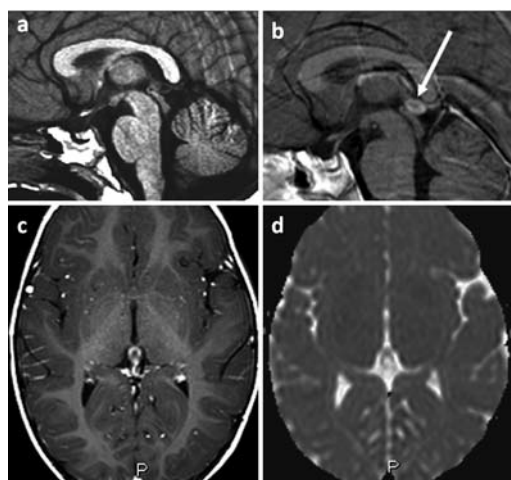


Figure 4. Patient 2 (third magnetic resonance imaging after 12 months). Sagittal (a) T1WI shows the cystic progression of the lesion, confirmed by (b) sagittal (arrow) and axial (c) contrast-enhanced images and by an increase of the value (d). Mild collapse of the gland is apparent, showing an enhancing wall more regular and thinner than before.

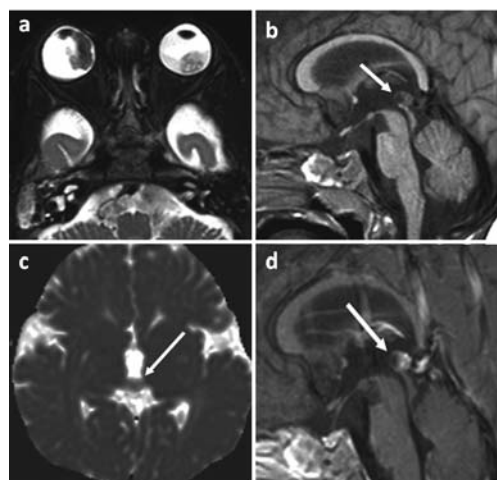


Figure 5. Patient 3. Axial T2WI (a) shows a bilateral. Sagittal SE T1WI (b) shows a 7-8 mm pineal lesion with an anterior small cystic component (arrow). The solid part of the lesion enhances after contrast medium (d) and presents a low ADC (c).

posterior solid part with low ADC, enhancing after contrast (Figure 5). Treatment was based on conventional chemotherapy (carboplatin/etoposide) and focal ophthalmic treatment with strict MRI follow-up. According to the MRI changes during the follow-up period, an intensification strategy based on carboplatin/etoposide/ifosfamide and double high-dose chemotherapy courses with busulphan/melphalan and thiotepa would be proposed. After the first course, the family returned to their country of origin and the patient died from progressive CNS tumour.

## Discussion

TRB represents a rare condition occurring in patients with RB, in most cases associated with familial history/bilateral presentation. Although different therapeutic options have been proposed for these patients, the outcome is almost invariably fatal (9, 11, 19-22). Recently, an intensive chemotherapy regimen, with or without radiotherapy, has been suggested to result in disease control in selected patients (18, 23).

Chemotherapy for RB may prevent TRB occurrence (6), this explaining the decreased incidence of TRB reported in the most recent series (14, 24). Moreover, this lower incidence was also due to a declining use of external-beam radiotherapy (25).

Recently, the medical debate has been focused on the MRI diagnostic criteria and the impact of early detection of intracranial lesions on survival (14, 15, 25). Moreover, the true incidence of metachronous TRB has probably been

overestimated due to an absence of routinely performed baseline MRI (14).

We report a single-Center experience over 14 years during which brain MRI was systematically performed at diagnosis or at the time of patient referral. The trend in declining incidence of TRB was confirmed in our series, as it occurred in 2.8% of the 107 investigated patients with RB. Moreover, TRBs were present in 6.7% of bilateral RBs and 6.7% of familial RBs, while none was reported in the unilateral RB group. Indeed, literature, reported that TRBs are present in fewer than 0.5% of patients with sporadic RB (5), while they occurred in 5-13% of cases of sporadic bilateral RBs and in 5-15% of familial bilateral RBs (9).

As reported above, chemotherapy prevents TRB occurrence. Since 2000, a conservative strategy with an extensive use of chemotherapy has been pursued at our Institution, mainly for bilateral RBs; this likely contributes to the low incidence of TRB. Moreover, our data confirmed the well-known increased risk of developing TRB in hereditary cases and in sporadic bilateral RB. The TRB occurrence rate in our groups was at the lower end of the range reported in the literature, confirming the suggestion that chemotherapy has a protective role.

Furthermore, it is our opinion that synchronous occurrence seems to be the most common presentation of TRB. As suggested by Rodjan *et al.* (14), we showed that metachronous TRB is probably an overestimated entity, as most patients with TRB are found to have a pineal/suprasellar mass at time of diagnosis if a baseline MRI is performed.

All patients with TRB in this report were younger than 18 months and had intracranial lesions of size 15 mm or less. The median age reported by Kivela (9) and by Rodjan *et al*. (14) was 26 and 23 months, respectively, while the lesion size was a median of 30 mm while the mean value of 29,7 mm for Rodjan. Our series confirmed a younger age at diagnosis of TRB and that an earlier baseline MRI allows detection of smaller intracranial lesions. Although the MRI screening program seems to identify smaller pineal gland lesions in younger patients, the protective role of early detection on survival is not proven.

Moreover, the clinical management of a small pineal gland lesion in a young asymptomatic patient with RB can be difficult, especially in the absence of histological findings. The MRI diagnosis criteria are subject to debate. Nevertheless, as being strongly suggestive of TRB, we considered the markedly enlarged size of the gland, particularly when necrotic changes are present, an irregular ring enhancement of its cystic wall, and the decrease in size associated with regressive changes of the MRI appearance of the gland after RB therapy. A progression of disease at strict MRI follow-up, as in the metachronous case, or changes in imaging during treatment confirmed the correct diagnosis. We would underline that during the study period, seven benign pineal cysts (6.5%) were diagnosed and none presented progression during the follow-up period.

However, the diagnostic work-up and clinical management of pineal lesions of less than 15 mm represent a challenge, particularly in synchronous presentation. In the presence of imaging aspects suggestive of TRB, a histological confirmation should always be considered, mainly in synchronous presentation. In metachronous presentation, a strict MRI surveillance seems the best option for avoiding overdiagnosis and subsequent aggressive treatment. Further analysis on large and multicentric trials should address how to consider a small synchronous pineal lesion suggestive of a TRB in bilateral or familial RB. A multidisciplinary team should be involved in order to address this question correctly, avoiding overdiagnosis and overtreatment, as well as surgical morbidity and mortality.

Our study suffers some limitations due to the relatively small number of patients and lack of a histologically-proven diagnosis. Nevertheless, in our series, a reduced incidence of TRB, mostly metachronous TRB, is clearly evident and is in agreement with previous reports (9, 14, 24).

Further analysis on large series and multicentre studies are required to confirm and clarify the best approach to small pineal gland lesions suggestive of pineoblastoma, focusing on the role of MRI and in the absence of a histologically-proven diagnosis. When a histologically-proven diagnosis is not available, a suspected diagnosis should be considered with caution and only follow-up will confirm the diagnosis. A wait-and-see-approach should therefore be considered.

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