TRILATERAL RETINOBLASTOMA: A LITERATURE REVIEW, 1971-2004

MOURATOVA T.

ABSTRACT

This study analyzes modern views on the history, variants, age at diagnosis of trilateral retinoblastoma, median time from retinoblastoma to trilateral retinoblastoma, the largest size and percentage of trilateral retinoblastoma among retinoblastoma cases, functions of pineal gland, genetics, ocular and intracranial histology, diagnosis, treatment, therapy results, survival rates and frequency of screening of trilateral retinoblastoma.

RÉSUMÉ

L'étude présente analyse les points de vue modernes sur l'histoire, les types et l'âge du diagnostic du rétinoblastome trilatéral, le temps moyen entre un rétinoblastome et un rétinoblastome trilatéral, la plus grande dimension et le pourcentage du rétinoblastome trilatéral parmi les cas de rétinoblastome, le fonctionnement de la glande pinéale, la génétique, l'histologie oculaire et intracrânienne, le diagnostic, le traitement, les résultats de la thérapie, les taux de survie et la fréquence de screening pour un rétinoblastome trilatéral.

KEY WORDS

Trilateral retinoblastoma. Diagnosis. Therapy and treatment results. Survival. Screening.

MOTS-CLÉS

Rétinoblastome trilatéral. Diagnostic. Thérapie et résultats du traitement. Survie. Screening.

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Retinoblastoma (RB) is a malignant tumour of the retina that is mainly found in children. The incidence of RB reported in the literature ranges from 1:10,000 (9) to 1:34,000 (69). Many authors found no difference in RB incidence among males and females. RB is the most frequent malignant eye tumour in children (59, 60) and can be unifocal or multifocal (31), hereditary or non-hereditary, familial or sporadic, unilateral, bilateral and trilateral (TRB).

History of TRB. TRB was first reported in 1971 by Jensen et al (33). Meur et al (56) described an infant girl aged 10 months with RB of the left eye and a suprasellar tumour which had "de rares rosettes". In 1977, Jakobiec et al (32) reported about 2 patients. The authors found that patients who develop symptoms of a brain tumour after a prolonged interval since the treatment of their ocular tumours should be suspected of harbouring a second intracranial primary.
In 1980, this association was termed TRB by Bader et al (5) who later described 11 patients with bilateral RB presented at a mean age of 6 months and with a pineoblastoma at 4 years (6). After these reports were published, a number of case reports appeared (2, 19, 20-23, 62-64, 74, 83-85, 87-89) that recognized TRB as a very rare condition (3, 10, 16, 34, 37, 51, 65, 86), with most cases almost always considered fatal (3, 10), lethal (10, 63) or the disease with a very poor outcome (35). However, recently several more optimistic reports were published that will be discussed below.

Variants of TRB. Since Bader et al (5) termed TRB as a combination of bilateral RB with pineoblastoma more than 20 years ago, some authors demonstrated that TRB can also be found in association with unilateral RB (14, 16, 18, 30-32, 39, 40, 79, 81, 89) or occur without

intraocular RB (18, 39, 40). One of the first TRB cases was found in a patient with a unilateral RB (56).

Pineal gland. The mammalian pineal shows circadian oscillations, but these damp out within a few days in the absence of input from the primary circadian pacemaker in the suprachiasmatic nuclei (48). In both diurnal and nocturnal vertebrates, including humans, its main product, the hormone melatonin, is synthesized and released in rhythmic fashion during the dark portion of the day-night cycle (44). Melatonin administration also has mild hypothermic and hypotensive effects and melatonin has been shown to be a powerful antioxidant (48). The two central effects of melatonin, photoperiodic time measurement and circadian entrainment, are probably mediated through completely separate mechanisms (28). Melatonin, the major product of the pineal gland, is also synthesized in the retina of several vertebrate species (82).

In certain lower animals, the pineal gland functions as a photoreceptor organ and resembles the retina histologically, and is described as a "third eye" (6). The tumour recalls the function of the pineal gland as a photoreceptor organ at an earlier stage of its phylogenesis (80). Animal pineal photoreceptors are functionally and morphologically similar to retinal photoreceptors (5). Primary tumours of the pineal gland or its vicinity may be classified into the tumours of parenchymal, interstitial or germ cell origin (12, 17). The WHO classification of the central nervous system neoplasms divides pineal parenchymal tumours into pineocytoma, pineoblastoma and mixed pineocytoma-pineoblastoma (25, 42). Neoplasms arising from interstitial cells represent astrocytomas. Pineoblastoma, a poorly differentiated neoplasm, occurs in childhood, whereas pineocytoma is better differentiated and occurs in adults (55).

In the literature, the tumours of the pineal gland or its vicinity are referred to as primitive neuroectodermal tumours (PNET) (8, 51, 71, 80), intracranial primitive neuroectodermal tumours (15, 65), pineal parenchymal tumours (PPT) (25, 55), midline intracranial malignancies or neoplasms or tumours (18, 26, 31, 66, 67, 77), intracranial tumours or neoplasms or malignancies (2, 13, 20, 30, 32), midline pineal tumours (71), pineal neoplasms or parasellar lesions (7), suprasellar RB (14), sellar tumours (16), pinealoblastoma (18, 31, 57, 75), pinealoma (23, 36, 46), pineal neuroblastic tumours (PNT) (41), pineal RB (34), ectopic RB (37, 39), ectopic intracranial RB or ectopic intracranial neuroblastic tumour (EINT) (39, 40, 83, 91), primary intracranial neuroblastic tumours (43), intracranial neuroblastic tumours or neoplasms (73, 81) or primary malignant intracranial tumours (76). The cerebral neoplasm can arise within the vermis as a medulloblastoma (24) or within the third ventricle of patients with TRB (37). Patients with "sellar" TRB have characteristics different from those of the patients with a pineal region TRB: the intracranial mass

Table 1: *TRB in RB patients over a research period of 10 years and more*

Authors	Country	City	Year of publication	Research period	RB cases	TRB cases	TRB percentage of RB
Amoaku et al (3)	UK	Birmingham	1996	1957-1994	146	5	3.4
Azar et al (4)	Australia	Sydney	2003	1975-2001	123	2*	1.6
Blach et al (11)	US	New York	1994	1979-1990	117	6	5.1
De Potter et al (18)	US	Philadelphia	1994	1972-1992	440	13	3.0
Helveston et al (29)	US	Indianapolis	1987	1967-1987	74	1	1.4
Kingston et al (39)	UK	London	1985	1954-1984	630	12	1.9
Kopelman et al (43)	US	New York	1987	1922-1959	361	2	0.6
Provenzale et al (67)	US	Durham	2004	1985-2002	63	8*	12.7
Scott & Richard (71)	US	Oklahoma	1993	1970-1990	56	3	5.4
Wu et al (90)	China	Guangzhou	1993	1986-1991	52	1	1.9
				Total:	2062	53	2.6

* There is no information about the number of TRB patients after 1999.

Table 2: *Cases of TRB analyzed in the literature from 1966 to 1998*

Authors	Country	City	Year of publication	Research period	TRB cases
Kivelä (40)	Finland	Helsinki	1999	1966-1998	106
Marcus et al (51)	US	Augusta, Georgia	1998	1971-1997	80
Paulino (65)	US	Maywood, Illinois	1999	1971-1997	94

Table 3: *New cases of TRB reported from 1999 to 2004*

Authors	Country	City	Year of publication	TRB cases
Amare et al (2)	India	Bombay	1999	1
Bindlish & LaRoche (10)	Canada	Halifax	1999	1
Cho et al (16)	Korea	Seoul	2002	1
Elias et al (24)	US	Charlottesville	2001	1
Halperin (27)	US	Durham	2000	2
Ibarra & O'Brien (31)	US	San Francisco	2000	1
Jubran et al (35)	US	Los Angeles	2004	3
Kivelä et al (41)	Finland	Helsinki	2003	1
Shields et al (73)	US	Philadelphia	2003	1
Taşdemiroğlu (84)	Turkey	Istanbul	1999	1

more often presents initially and occurs at a younger age. It is more common in females and is more often associated with unilateral ocular lesion (8). In TRB, pineal tumours are comparatively more common than suprasellar and parasellar tumours (2, 3, 6, 18, 30, 66), but the origin of supra/parasellar and pineal tumours in RB patients is still questionable (2). The pineal region has the greater variety of tumour types (22). The pineal region tumours occur more frequently than suprasellar PNET (65) and suprasellar TRB was diagnosed earlier and may arise earlier than pineal TRB (40).

TRB in RB patients. According to Jubran et al (35) who performed a retrospective review of medical reports of all RB patients, TRB occurred in 15% of patients with RB. However, De Potter et al (18) found TRB in 3% of RB patients. In Table 1, this percentage varies between 0.6% (43) and 12.7% (67).

In a total number of RB cases (2062 cases), TRB occurs in 2.6% (53 cases). Most cases of TRB (33 cases) were found in the US. Some of these (Table 2) (11, 13, 14, 70, 80, 88) have not been analyzed by Kivelä (40), the other cases (3, 7, 8, 21, 37, 62, 64, 68, 70, 77, 78, 90) have not been analyzed by Marcus et al (51), and some cases (21, 37, 46, 78, 80, 88, 90) have not been analyzed by Paulino (65). Some cases (2, 10, 16, 24, 27, 31, 43, 84, 87) have not been included in the analysis either by Kivelä (40) or Marcus et al (51) or Paulino.

From 1999 to 2004, 13 new cases of TRB were reported in various countries (Table 3), of which the majority cases of TRB (8 cases) were reported in the US (24, 27, 31, 35, 73).

Gender. Of children, who developed TRB, 41.5% (65) or 48% (40) were boys, and 52-53.2% (40, 61) were girls. The male-to-female ratio of children who later developed a PNT was similar to that of those who developed an ectopic intracranial tumour (40, 51).

Age at diagnosis of intraocular RB. Most cases are diagnosed in the 0-4 age subgroup, with the peak incidence in the second year of life (61). The median age at diagnosis of RB was 5-6 months (40, 65), and the median age at diagnosis of bilateral RB was 4,5 months (67). Age at diagnosis was younger for children with familial RB compared to age at diagnosis of children with sporadic RB (40).

Age at diagnosis of TRB. The median age at diagnosis of TRB was 26 months (67) or 30,7

months (51). There was no difference between median age at diagnosis of children with unilateral and bilateral RB or between those with familial and sporadic RB (40).

The median time from RB to TRB was 21-22 months (18, 40, 65). The time of TRB was longer for pineal tumours than for suprasellar tumours (40). The time of diagnosis of RB varied between 5 months after the intracranial tumour was diagnosed and 4 years before the intracranial tumour was diagnosed (66). An average interval between RB and TRB diagnosis was 24,6 months (51). A latent period of one to several years is typical between the appearance of RB and TRB (40).

Laterality of RB. Bilateral RB was found in 86% to 89% of children with TRB and only 11-12% of children with TRB had unilateral RB (40, 51, 66). Of 8 children with TRB and bilateral RB, none had unilateral RB (67). A case of unilateral RB with a sellar and suprasellar mass which was considered TRB has been reported (16, 31).

Family history for TRB. Most authors found a positive family history of RB in patients with TRB (40, 51, 52, 65, 66) but only 3 patients out of 207 patients with RB had TRB and none had a positive family history of RB (35). Children with familial RB have a particularly high incidence of TRB (11, 18, 30, 34, 46). The chances of TRB development were less than 0.5% among unilateral RB, 5% to 13% among sporadic bilateral RB, and 5% to 15% among familial RB (11, 13, 39, 40, 71).

Genetics. "The gene responsible for RB is located at 13q14" (41, 45). This gene can mutate or delete in both nonheritable and heritable forms of RB (6, 51). RB may occur as a germinal mutation or a somatic mutation. Forty percent of RB cases are caused by a germline mutation and include patients with a positive family history of RB (31). An insertion of the q12.3q21.3 segment of chromosome 13 into chromosome 18 at band q23 in a patient with RB was identified in family members of a patient with TRB (24). The direct transmission of an RB1 allelic loss from a phenotypically normal mother to a RB child was detected (2). The specific marker chromosome i(6p) has been found in 9 tumours of 15. In 2 cases, trisomy of the short arm of chromosome 6 was present (45), but normal chromosomes were found in a case of a hereditary bilateral RB and pinealoma (23). There is no difference between children with mosaic and non-mosaic chromosomal deletion of 13q14. Only 7% of 29 patients who had a mosaic chromosomal deletion, including 13q14 did not develop TRB (11, 39, 40), but it is not known which proportion of those who had mosaic deletion did (41). Whenever a 13q14 deletion is diagnosed, immediate ophthalmologic evaluation is recommended to ensure prompt diagnosis of RB (41).

Size of TRB. The median largest dimension of PNT (77%) and EINT (23%) was 30 mm, 18% were 15 mm or less in size and 35% were between 16 and 30 mm in size. The size of PNT and EINT did not differ in children who were not screened. Of 15 TRB detected at screening, 33% were 15 mm or less in size and 10% of patients with TRB were detected after symptoms developed (40).

Ocular signs and symptoms. Patients with TRB presented with decreased visual acuity (51), leucocoria (77, 41), nystagmus (8, 16, 84), ophthalmoplegia (51), strabismus (89), proptosis with signs of bilateral glaucoma (88), microphthalmia (56), microphthalmia, coloboma of the iris, choroid and retina (52), a large vitreous seeding (41), a vascularized fluffy white mass in the posterior pole (52), "glow" in the eye (77), and papilledema (51).

Signs and symptoms of increased intracranial pressure. Patients with TRB (35, 46, 47, 57, 89) presented with headache, nausea, vomiting and lethargy (84), irritability (8), tendency to opistothonus (41), hydrocephalus (7, 8, 22, 46), hydrocephalus and seizures (52), críses épileptiformes (flush, transpiration et fixité du regard) (56) and somnolence (18). Sixth nerve palsy, ataxia, progressive weakness, personality change, upgaze paralysis, sweating, pyrexia, and constipation were less frequent (51). Some patients could be asymptomatic and the intracranial mass was discovered on screening CT or MRI (47, 51, 87).

Diagnosis. Ophthalmologic examination, echography (ultrasonography), CT and MRI were used to confirm the diagnosis of TRB (2, 3, 20, 51, 68, 75, 77, 84, 90, 92), for diagnosis of a primary or metastatic neoplasm in the brain or spinal metastases (51, 67, 75) and for identifying the previously irratiated volume and minimizing reirradiation of that volume (50). MRI showed the presence of the pineal region tumours that had no evidence of tumour on CT scan (22). As calcification may be the only clue for the presence of the intracranial malignancy, close surveillance of high-risk patients with initial CT and follow-up MRI images is suggested (2, 7, 8). Both CT and MRI may demonstrate the appearance of a primary or metastatic neoplasm in the brain and of spinal metastases (67). An intracranial neoplasm of asymptomatic patients can be found through routine brain-imaging studies (18). Bone marrow aspiration and lumbal punction are not suggested as routine investigation (4).

Tumour markers. Attempts were made to find out tumour markers by analyzing human chorionic gonadotropin (hCG), alpha-feto protein (AFP), carcinoembriotic antigen (CEA) and lactic dehydrogenase (LDH) in blood and cerebrospinal fluid (CSF). Only LDH was elevated and hCG, AFP and CEA were normal. If LDH level in CSF is elevated, the patient should be periodically monitored by non-invasive imaging of the brain to detect intracranial tumour at an early stage (78). AFP and hCG were helpful in determining the presence of malignant germ-cell tumours, particularly those with a poor prognosis (22). A small number of tumour cells showed positive immunostaining to retinal S-antigen (70, 85). None of the tissues examined were found to contain retinal S-antigen or P-antigen (19).

Ocular histology. The ocular histology in patients with TRB in 38 cases of 80 showed small, undifferentiated cells with large basophilic nuclei and scant cytoplasm. Areas of calcification and necrosis with perivascular preservation of cells and photoreceptor cell differentiation with Flexner-Wintersteiner rosettes or fleurettes were frequently noted (88). Two cases demonstrated a well-differentiated tumour in one eye and a poorly differentiated tumour in the contralateral eye. Invasion beyond the lamina cribrosa was never observed (51).

Intracranial histology. The intracranial tumours were described (51) as primitive or undifferentiated tumours, tumours with "some early signs of differentiation", undifferentiated tumours with "rosette clusters unlike Flexner-Wintersteiner rosettes", tumours with rosettes and possible fleurettes, a tumour with Homer-Wright rosettes, and tumours with Flexner-Wintersteiner rosettes. In summary, authors found that of 26 cases in which CNS histopathology was described, 61.5% were undifferentiated and could be considered as PNET (51). Flexner-Wintersteiner rosettes and Homer-Wright rosettes were also observed (16, 56). Pathologically, the pineal tumour is indistinguishable from an ocular RB (34).

Differential diagnosis. In a child with intracranial tumour and history of RB, the differential diagnosis includes intracranial extension of an ocular RB and second nonocular primary CNS tumours. Second intracranial tumours in patients with heritable RB are divided into those within the field of radiation and those outside the field of radiation (51). Within the field of radiation, osteosarcoma, soft-tissue sarcoma, glioblastoma, astrocytoma and neurofibroma may be observed, but may be distinguished from TRB by radiological diagnosis (51). Outside of the field of radiation, osteosarcoma, pinealoma, astrocytoma, and neuroepithelioma may be observed (1). A great variety of tumour types is found in the pineal region (22). The ultimate differentiation between PNET, intracranial RB, pinealoblastoma, and ependimoblastoma is difficult (51). Detached and dysplastic retina, subretinal blood, Coats' disease, "sclerosing endophthalmitis", and vitreous and subretinal exudates may be identified by CT (38).

Treatment. As the great variety of tumour types found in the pineal region must be treated in different ways (22), the treatment for this rare subtype of RB remains to be established (2). The treatment of PPT varies, regardless of the disease stage, from surgery or radiotherapy alone to combined treatment with surgery, radiotherapy and chemotherapy. Moreover, techniques

advocated are numerous: from stereotactic biopsy to complete tumour resection for surgery, from radiosurgery to craniospinal irradiation for radiotherapy (11, 22, 25, 50, 63). Radiation therapy ranged from 20 to 59,2 Gy to the primary tumour and from 30 to 41 Gy to the craniospinal axis (51) or 55 Gy directly to the primary tumour and 30-36 Gy to the craniospinal axis (30) or 45 Gy over 15 fraction in 25 days to the hole cranium with suprasellar radiation boosted to 55 Gy with paired lateral ports (2). Surgical treatment such as subtotal resection of the sellar-parasellar mass (8), subtotal craniotomy with gross total resection of the suprasellar mass (35, 77), intratentorial suboccipital craniotomy (41), subtotal removal of pineoblastoma (89) and surgically excision of tumour by transventricular approach (37) with radiation and/or chemotherapy is suggested (6, 14, 19, 23, 26, 34, 35, 49, 57, 66, 67, 89, 92). Platinum-based chemotherapy with intrathecal therapy (2, 51), vincristine and cyclophosphamide (49, 63), ifosfamide, carboplatine, and etoposide (77), intrathecal methotrexate, hydrocortisone, and cytarabine (29, 63), methotrexate, cytosine arabinoside, and hydrocortisone (2) were used. For the last 4 years, chemotherapy or chemoreduction as a treatment of patients with TRB is used with carboplatin, etoposide, and vincristine (54, 72, 73), cytoxan, vancomycin, and adriamycin (16), vincristine, lamustine, and prednisolone, combined with intrathecal methotrexate, cytarabine and prednisolone (41), cyclophosphamide, etoposide, and thiotepa, followed by autologous bone marrow transplant (35, 67).

Treatment results. Marcus et al (51) analyzed the results of treatment of 57 patients with TRB described in the literature (Table 4).

In spite of the small number of patients in each group, chemotherapy alone was the most successful method because the average survival time was the longest (24,6 months) and percentage of living patients was the highest (42.9%). Successful chemotherapy treatment for patients with TRB was described by various authors (54, 63, 72, 73). For the past 4 years, chemoreduction with vincristine, etoposide, and carboplatine was used for more than 160 children with intracranial RB. Most of these children were bilaterally affected and would be at risk for TRB. None of these patients developed TRB, although based on published data one would have expected 5 to 16 patients to do so. In the same period of time, TRB has been seen in children who did not receive chemoreduction (72). For all 75 patients with TRB, the median survival after a diagnosis of intracranial tumour was 6 months (65). The median survivals for children with tumour of the pineal region and PNET of the suprasellar region both were 6 months. The median survival for children who received no treatment for the intracranial tumour was 1 month whereas it was 8 months for children who were treated for the intracranial tumour. Death from an intracranial neoplasm occurred at a mean 11 months after diagnosing that tumour (18). The causes of death were: disseminated neuroaxis disease (65), leptomeningeal tumour dissemination despite lack of progression in the midline intracranial mass (67, 77), diffuse central nervous

Table 4: *Treatment results of TRB reported in the literature (51)*

Methods of treatment	Chemo therapy alone	Chemo-therapy with intrathecal therapy	Chemo-therapy including cisplatine or carboplatine	Radiation therapy to the primary tumour and craniospinal axis alone	Radiation with chemo-therapy without surgical intervention	Radiation and/or chemo-therapy with surgical resection/ craniotomy
Average survival time, months	24.6	19.8	7.2	6.5	11.7	11.1
Number of patients	7	14	5	10	23	14
Number of patients alive at the time of publication	3	4	1	-	1	2

system tumour (21, 52), subsequent spread of tumour to other sites within the central nervous system (39), concurrent or subsequent subarachnoid dissemination (7), sepsis without evidence of metastasis or leptomeningeal spreading (16), and consequences of intrathecal chemotherapy (29). The most serious complication of anaesthesia was a case of enterobacterial cloacae sepsis (27). Cranial and spinal leptomeningeal metastases were invariably followed by a lethal outcome (67); metastases can also occur in the ulna (67).

Screening. Screening is only useful when the screened disease is treatable and the rate of incidence is high. Both conditions may not be met in patients with TRB (58). The recommendation of routine screening with imaging studies for early detection of TRB is questionable (31) as the low incidence of TRB may not warrant routine imaging and would not be physically or economically practical (39, 53, 54) unless pertinent signs are present (30, 69, 91). One half of TRB cases detected by screening were found at baseline and one quarter was found during the following year (40). It could be rational to screen every 3 months during the first year of diagnosis of RB (53, 63) or every 6 months until the age of 2 years and early until the age of 4 years (18) or twice a year for the next 3 years (40) or every 3 months for the first 2 years, every 4 months for the next 2 years and then every 6 months until the age of 5 years (63, 76, 84). Routine ophthalmoscopy of patients with suprasellar PNET and other atypically located PNET may reveal more cases of sellar TRB and hereditary RB (8, 16). As TRB is nearly always observed in hereditary RB (bilateral or multifocal or a positive family history), screening efforts should be applied to the at-risk cohort (11, 76). When screening was performed, median survival after TRB was significantly longer. The actuarial survival of screened children stabilized at 27% after 5 years by which time all those who had not been screened were dead of TRB (40). Screening is recommended for intracranial tumours in children with bilateral and/or familial RB until 4 years (18) because 89% of patients will have developed an intracranial tumour 4 years after the initial diagnosis of intracranial RB (65).

CONCLUSION

TRB occurs in 4% of patients and is diagnosed more commonly in patients with the bilateral disease who are less than 1 year of age (35). The pineal tumours are comparatively more common than suprasellar and parasellar ones (18, 66, 68). The true incidence of TRB, particularly that with suprasellar involvement, is unknown (77). In 2062 patients with all forms of RB described in the literature, TRB was found in 2.6%. TRB with pinealoblastoma and TRB with supra/parasellar tumours are now recognized as two distinct entities due to differences in their presentation and prognosis (2, 3, 18). The origin of supra/parasellar and pineal tumours in RB patients is still a query (2). Chromosomal and genetic mosaicism consequently is a phenomenon that every physician who manages patients with RB must understand. These children may benefit from prompt ophthalmologic examination because RB is the main or perhaps the only life-threatening association of 13q-deletion syndrome (41). An occult RB is reported to have escaped the attention of the radiologist, paediatrician, geneticist, and paediatric neurologist who had an opportunity to review the scan and who knew about the 13q-14 deletion (41).

The optimal therapy for patients with TRB is still not known but over the past 20 years, the treatment for TRB has progressively resulted in increased survival of patients (51). Effective treatment of TRB may require close evaluation of these children for leptomeningeal dissemination (67). Furthermore, spinal metastases can be present in the absence of obvious intracranial leptomeningeal dissemination. Hence, routine performance of both cranial and spinal MRI appears reasonable for patients with TRB, even when an intracranial mass is initially diagnosed (67). A decreasing frequency of enucleation and an increasing tendency to use eye-preserving methods of management have been documented (75).

From 1999 to 2004, 13 new cases of TRB were reported in the literature. Despite intensive research of TRB, there are a number of unclear issues concerning this rare disease with predominantly fatal outcome such as unknown incidence rate, the origin of supra-parasellar and pineal tumours in RB patients, the opti-

mal therapy and treatment regime, time and frequency of screening, causes of gene mutation, etc.

It is hoped that re-evaluation of treatment plans and concepts regarding the histogenesis and molecular basis of TRB will extend the length of survival in these children (51), and efforts will be made to standardize the treatment (47). With the availability of newer chemotherapy regimens, the prognosis of TRB patients may improve in the future (76). Larger studies are needed to determine risk factors and the optimal therapy (35).

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Request for reprints and correspondence:
Prof. Dr. Tamara MOURATOVA
Dendermondesteenweg 9/11
B-9230 Wetteren
Belgium
E-mail: tatumur@lycos.com