

# Development of Progressive Chiari I Malformation in a Child with Unilateral Sporadic Retinoblastoma

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## Abstract

**Purpose:** To report a case of progressive Chiari malformation type I (CIM) in a patient with unilateral sporadic retinoblastoma (RB) treated with intra-arterial chemotherapy (IAC) and enucleation.

**Methods:** A 5-year-old male patient with a history of RB in his left eye treated with IAC and enucleation presented to our clinic for routine RB surveillance. Radiotherapy had not been used for the treatment of his RB.

**Results:** A progressive herniation of cerebellar tonsils through the foramen magnum was detected on follow-up magnetic resonance imaging (MRI). Brain and cervical MRI revealed no central nervous system mass, hydrocephalus, or syringomyelia. There was no history of head trauma.

**Conclusion:** Progressive CIM may occur in unilateral sporadic RB.

**Keywords:** Chiari malformation, Chiari malformation type I, Germline, Intra-arterial chemotherapy, Posterior fossa, Retinoblastoma, Sporadic

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## INTRODUCTION

Chiari malformation type I (CIM) has been described as herniation of the cerebellar tonsils through the foramen magnum (>3 mm) in the pediatric population.<sup>1,2</sup> An imbalance between the growth of posterior cranial bone and posterior central nervous system (CNS) is known to be the etiology of CIM. This condition often becomes symptomatic during late childhood. The most frequent presenting symptom is headache within the posterior fossa region.<sup>3</sup> Association between unilateral retinoblastoma (RB) and CIM has never been reported in literature.

Herein, we report a case of unilateral sporadic RB with progressive CIM. Magnetic resonance imaging (MRI) scans for RB surveillance revealed ectopic cerebellar tonsils.

## CASE REPORT

A 5-year-old male patient with a history of RB in his left eye presented to our clinic for routine RB surveillance. The patient was diagnosed with unilateral sporadic RB, which had been manifested during his 2<sup>nd</sup> year of life. He had received multiple sessions of intra-arterial chemotherapy (IAC) with melphalan and topotecan. Because the RB tumor had not regressed, he had undergone enucleation of the left eye when he was 3 years old. Since then, he has been followed up with scheduled brain MRI for RB surveillance according to standard protocol. Despite the initial normal MRI reports, gradual descent of the cerebellar tonsils through the foramen magnum was reported in his MRI at a 4-year-old follow-up visit. The progression of CIM

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was confirmed by the radiologist in the last MRI, which was performed at 5 years of age [Figure 1]. There was no sign of CNS tumor, hydrocephalus, or CNS traumatic injury, and the patient did not have any history of intracranial surgery. Cervical spinal cord MRI was performed, and there was no pathologic finding, including syringomyelia. Neurological history and physical examination were performed by a neurosurgeon, where all findings were normal. The patient was followed up by neurology and neurosurgery service, and intracranial pressure has been reported to be normal following lumbar puncture analysis. Examination of his right eye was normal. The informed consent was obtained from the guardian.

## DISCUSSION

The causative pathology of Chiari malformations is thought to be congenital, while it may not be clinically manifested until adulthood. Rarely, a Chiari malformation may develop later in life. Supratentorial mass, craniosynostosis, CNS shunt therapy, acromegaly, and special types of rickets have been identified as the etiologies of acquired CIM.<sup>4</sup> None of these conditions was diagnosed in our patient. According to the normal reports of initial brain MRIs, the gradual onset of CIM in our patient seems to be in the 4<sup>th</sup> year of his life, where it is impossible to distinguish between late-onset congenital CIM and acquired CIM.

To discuss the etiology of RB and CIM coincidence, it is needed to evaluate the presence of germline mutation of RB. Association between RB and CIM has been reported in three cases in literature,<sup>5,6</sup> where all the three patients had RB secondary to germline mutations. Our case had unilateral sporadic RB, where the chance of the presence of germline mutation is as low as 15%.<sup>7,8</sup> When the germline mutation is present, the role of defected RB gene and protein should be considered the underlying cause of CIM. However, for those patients with somatic mutations of RB (the most probable condition in our RB patient), the etiology of CIM should be investigated among a wide range of possibilities.

The association between both idiopathic and acquired growth hormone deficiencies and CIM has been reported. In a case

report, it was postulated that acquired hypopituitarism following trilateral RB treatment during infancy can cause progressive CIM.<sup>9</sup> However, in our case, there was no history or sign of hypopituitarism.

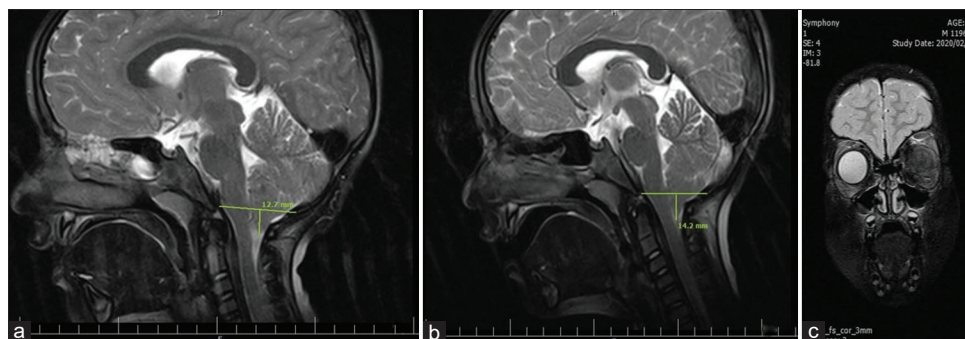
Cranial radiotherapy, a therapeutic option in RB patients, has been reported to cause progressive CIM.<sup>10</sup> However, this child did not receive radiotherapy.

Chemotherapeutic agents such as those used in this patient with RB can cause global slight defect of bone growth;<sup>11</sup> however, a sudden local arrest of bone growth to justify CIM development has not been reported.<sup>10</sup> In addition, in IAC, chemotherapeutic agents are delivered through ophthalmic artery, which theoretically cannot be associated with a high local concentration of therapeutic agents in the posterior fossa.

A possibility should be considered for the role of IAC technique in this case. The complications attributed to the technique of IAC include intraoperative endovascular complications related to internal carotid artery territory, while posterior fossa blood supply is provided through vertebrobasilar vasculature. Although there are some anastomoses between these two vascular systems in CNS, perfusion defect in posterior fossa following IAC seems to be of least probability.

For patients with germline mutation of RB1 gene, altered expression of RB1 gene may be hypothesized as a causative factor for CIM development. However, because the genetic basis of CIM development has not been clarified, it is difficult to find a common genetic pathophysiology for the coincidence of RB and CIM. Boyles *et al.* have identified two candidate loci on chromosomes 9 and 15 for genetic inheritance of CIM,<sup>12</sup> while RB gene is located on chromosome 13. The mutation of the RB gene is strongly associated with osteosarcoma formation. This association reveals that RB protein is an effective factor in bone development. Inactivation of RB1 gene has been reported to cause abnormal ossification of numerous bones, a pathologic mechanism which is related to a deficiency in osteoblast differentiation.<sup>13</sup> It may be postulated that mutated RB gene product plays a role in the development of progressive CIM in RB patients.

In the present case study, we reported the formation of a progressive CIM in a patient with unilateral sporadic RB. An



**Figure 1:** T2-weighted midsagittal magnetic resonance imaging scans revealing a progressive Chiari I malformation in a patient with unilateral sporadic retinoblastoma treated by enucleation of the left eye. Basion–opisthion line is shown to determine the herniation of cerebellar tonsils through the foramen magnum at 4.5-year-old (a) and 5-year-old (b) visits. Orbital socket filled with hydroxyapatite is also shown (c)

association between RB and CIM requires to be confirmed through further reports and studies.

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Nil.

### **Conflicts of interest**

There are no conflicts of interest.

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