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Case Report/รายงานผู้ป่วย

Specific Ocular Findings Leading to the Diagnosis of Early-Onset Neurofibromatosis Type 2

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Abstract

Background: Neurofibromatosis type 2 (NF2) genetic disorder primarily characterized by the central nervous system tumors, including intracranial schwannomas and meningiomas.Diagnosis is often delayed due to variable presentations, especially in pediatric patients where ophthalmologic abnormalities may be the earliest sign.

Case Presentation: A 4-year-old boy referred for ocular evaluation due to multiple café-au-lait macules. Initial examination revealed reduced visual acuity, bilateral iris mammillation, and left retinal hamartoma, raising suspicion of NF2. Despite glasses being prescribed, the patient was lost to follow-up and returned at age 8 with left eye visual deterioration. Subsequent examination identified a flame-like epiretinal membrane (ERM) in the right eye and a combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) in the left eye. Magnetic Resonance Imaging (MRI) confirmed multiple cranial nerve schwannomas and a left optic nerve sheath meningioma (ONSM), confirming the NF2 diagnosis at age 10.

Discussion: Pediatric NF2 can present with distinctive ocular findings: cortical cataracts, ERMs, CHRRPE, and ONSMs, which may precede neurological symptoms. Early recognition of NF2 ocular signs is crucial for timely diagnosis and management, potentially reducing morbidity.

Conclusion: This case highlights importance of thorough ophthalmologic evaluation in NF2 children. Early diagnosis can guide appropriate multidisciplinary management, improving prognosis in pediatric NF2 patients.

Keywords: Retinal hamartoma, Pediatric ophthalmology, Optic nerve sheath meningioma, Neurofibromatosis Type 2, Neurofibromatosis, Pediatric neurofibromatosis

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Background

Neurofibromatosis type 2 (NF2) is a rare inherited disorder characterized by central nervous system tumors, predominantly intracranial schwannomas and meningiomas.[1] First described by Wishart in 1822 as a case of skull, dura mater, and brain tumors causing deafness[1], NF2 has an estimated incidence ranging from 1 in 25,000 to 1 in 87,410 live births[2-4]. Bilateral vestibular schwannomas are the hallmark of NF2, but patients are also prone to develop other tumors, including multiple meningiomas, gliomas, and neurofibromas[5-7]. Ocular lesions, neuropathies, skin surface tumors, and glial hamartia are additional characteristic manifestations[5-7]. Genetic studies have linked NF2 to mutations of the NF2 gene on chromosome 22q12, resulting in multiple tumor development in nerve sheaths, with over half of cases representing de novo mutations[5-7].

NF2 clinical courses are variable, ranging from early-onset multiple tumors to lifelong asymptomatic presentations[8,9]. Diagnosis primarily relies on magnetic resonance imaging (MRI), potentially supported by genetic confirmation of NF2 gene mutations. The 2018 revised Neurofibromatosis Type 2 Diagnostic Criteria, based on the Manchester criteria for NF2, aid in diagnosis[10]. However, definitive diagnosis can be delayed due to the rarity of NF2 and its diverse clinical manifestations. Older adolescents and adults typically present with vestibular schwannomas, while ophthalmologic abnormalities are common in children and young adolescents[11]. This case report illustrates the characteristic ocular features that may present at a young age without neurologic or auditory symptoms, resulting in a 6-year diagnostic delay in this instance.

Case Presentation

A 4-year-old boy, referred by a pediatrician for ocular evaluation due to multiple café-au-lait macules on all extremities, presented with visual acuity of 20/100 in the right eye and 20/60 in the left (picture chart). Anterior segment examination revealed bilateral iris mamillation and a left focal cortical cataract. Fundus photography showed normal optic discs bilaterally, a right epiretinal membrane (ERM), and a left retinal astrocytic hamartoma (Figure 1A). Glasses were prescribed according to cycloplegic refraction (right eye, -1.00 -0.50 X 20; left eye, -1.50 -2.50 X 145), after which the patient was lost to follow-up.

During this period, the patient underwent bilateral lateral rectus recession for exotropia at a private hospital at age 6. At age 8, he returned to the eye clinic due to gradual vision loss in the left eye. Examination revealed finger-counting visual acuity in the left eye, a focal cortical cataract, and a relative afferent pupillary defect in the left eye. Fundus photography showed a pale disc and retinal hamartoma in the left eye, with an ERM in the right eye (Figure 1B).

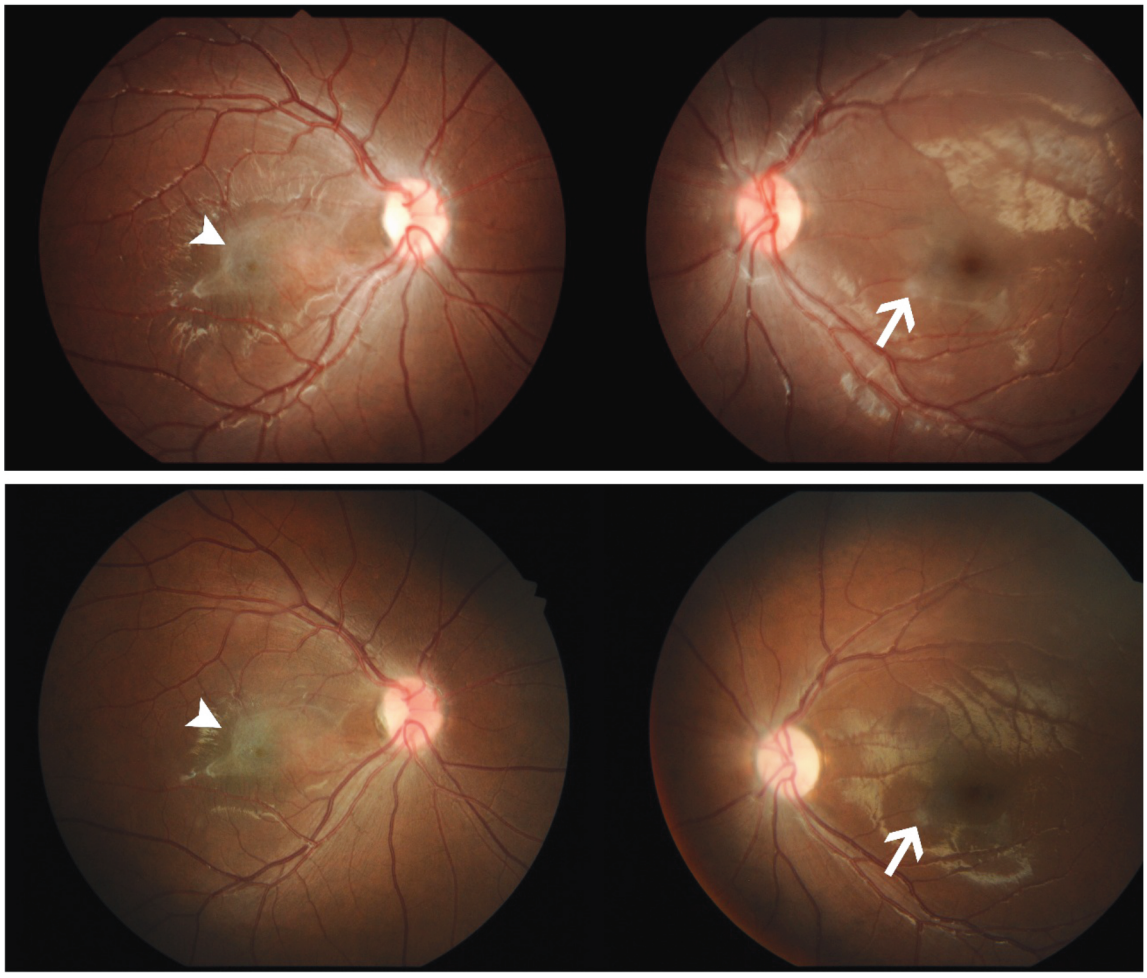

Figure 1 (A) Initial fundus photography of a 4-year-old boy showing an epiretinal membrane (arrowhead) in the right eye and a retinal hamartoma (arrow) in the left eye. (B) Fundus photography at age 10 years depicting an epiretinal membrane (arrowhead) in the right eye, along with a pale optic disc and a retinal hamartoma (arrow) in the left eye.

Investigations

Spectral-domain optical coherence tomography revealed a unique, flame-like ERM pattern in the vitreous of the right eye and a combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) in the left eye (Figure 2). As NF2 was suspected, the boy was referred to the hospital's genetic clinic for further evaluation. He reported no hearing or neurological problems, and there was no family history of neurofibromatosis. Although his mother had nonspecific café-au-lait macules, she lacked other neurofibromatosis-associated symptoms.

MRI of the brain and orbits revealed multiple enhancing masses in bilateral cranial nerves (CN) V, right CN VI, bilateral CN VII, bilateral CN VIII, bilateral CN IX, bilateral CN X, and bilateral CN XI, suggestive of multiple schwannomas. A left optic nerve sheath meningioma (ONSM), a meningioma to the right of the cervicomedullary junction, and pressure on the optic nerve and left extraocular muscles (especially the left inferior rectus) were also detected. This pressure caused atrophic changes in the left optic nerve with optic neuropathy.

Based on these clinical and investigational

findings, the patient met the NF2 diagnostic criteria[10], and a definitive diagnosis of NF2 was established at age 10. A multidisciplinary clinical evaluation (otolaryngologist, pediatric neurologist, and neurosurgeon) was initiated. An audiogram and other hearing tests were unremarkable.

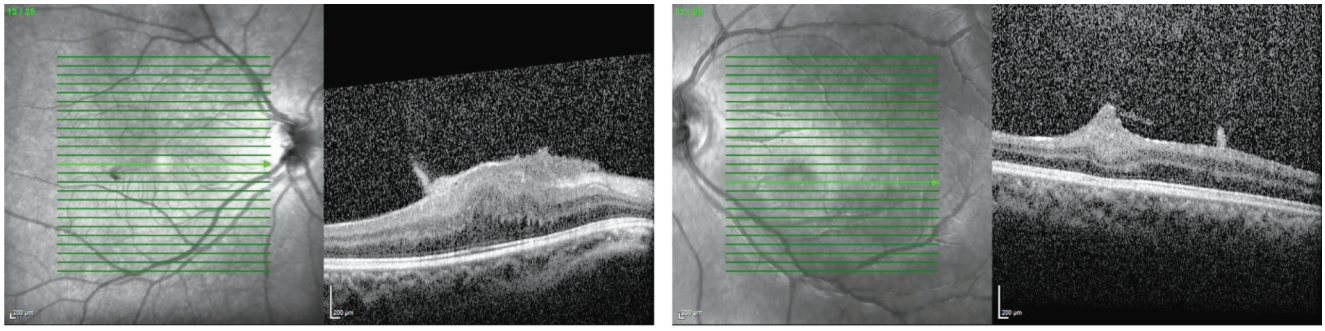

Figure 2 Spectral-domain optical coherence tomography illustrates the distinctive flame-like pattern of an epiretinal membrane extending into the vitreous in the right eye, and a combined hamartoma involving the retina and retinal pigment epithelium in the left eye.

Outcomes And Follow-Up

Due to the pressure effect of the meningioma involving the left optic nerve sheath, tumor removal was recommended to preserve left-eye vision. However, the patient's parents opted for close monitoring of the boy's symptoms instead.

Six months later, brain and whole-spine MRI (Figure 3) revealed increases in the sizes of the bilateral vestibular schwannomas, bilateral Meckel's cave schwannomas, right jugular foramen schwannomas, the cisternal part of right CN XII schwannomas, the left optic nerve meningioma, and the meningioma to the right of the cervicomedullary junction extending to the C2 level. Left eye proptosis was also noted. Subsequently, the boy underwent left frontotemporal craniectomy with gross total resection of the orbital and tuberculum meningiomas to protect left eye vision. There were no immediate postoperative complications. One-month postoperative MRI showed no obvious residual tumor and a 50% improvement in proptosis. Additionally, radiation therapy was administered for the vestibular schwannomas. Tumor removal at the foramen magnum is planned upon completion of radiotherapy.

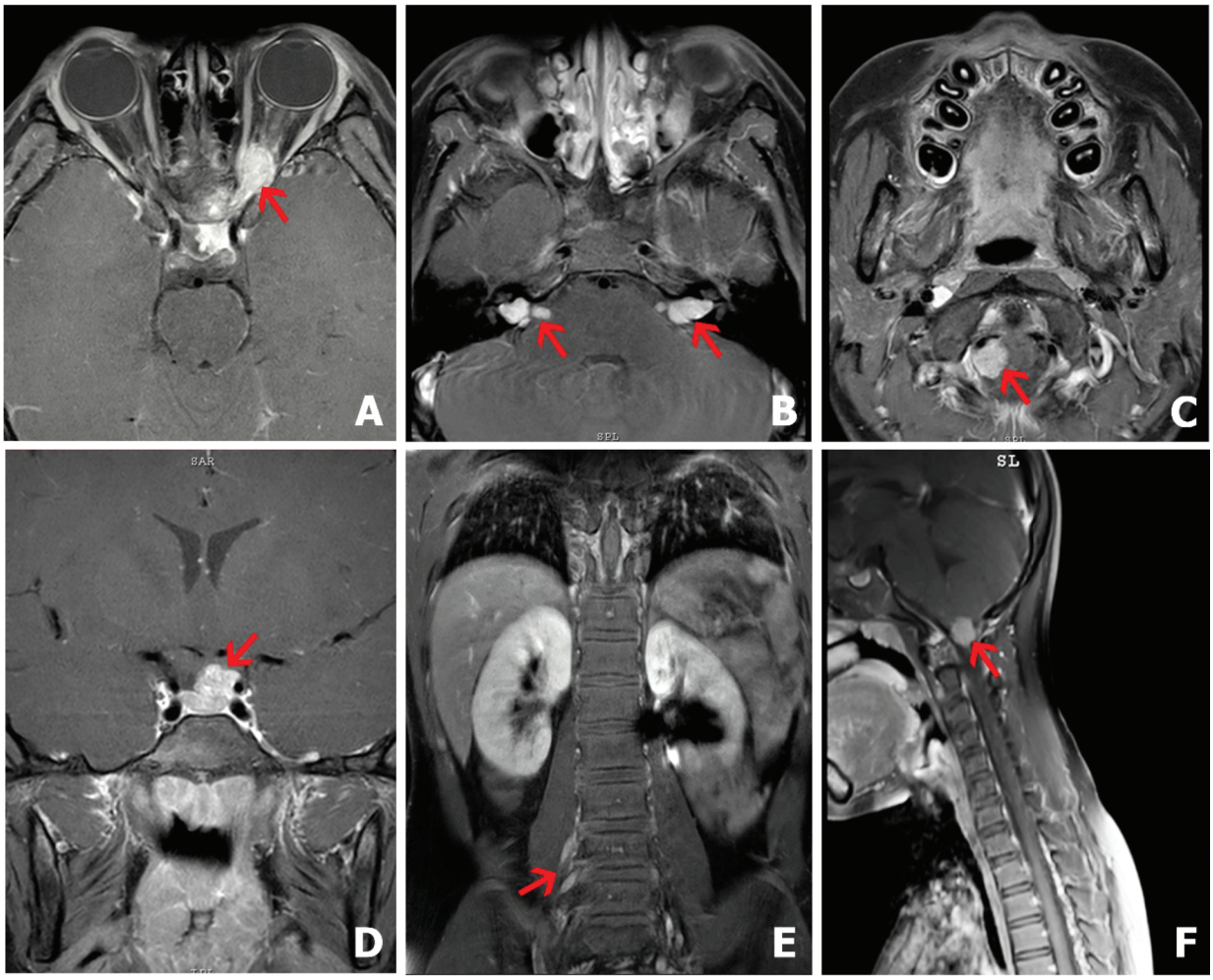

Figure 3 MRI T1-weighted images postgadolinium in axial and coronal planes demonstrate multiple tumors. (A) Left optic nerve sheath meningioma; (B) bilateral vestibular schwannomas (arrows); (C) right-sided meningioma at the cervicomedullary junction in axial and (F) sagittal views; (D) schwannoma on the left planum sphenoidale, partially extending to the pituitary fossa; and (E) meningiomas at the L4 and L5 nerve roots (arrows).

Discussion

NF2 is a rare, autosomal dominant disorder characterized by tumor predisposition. Early- and adult-onset NF2 exhibit distinct clinical presentations. Adult-onset NF2 typically manifests as hearing loss, tinnitus, or positional imbalance, indicative of CN VIII dysfunction[12-14]. Conversely, pediatric NF2 patients often present with nonvestibular nerve schwannomas (such as spinal cord tumors), extravestibular CN involvement, or ophthalmological symptoms[12-14]. Gugel et al. reported a median age of diagnosis of 11 years (range 1–17 years) for nonfamilial NF2, with ophthalmological manifestations being the most common presenting symptom (49%)[11].

The patient described in this case report, a 4-year-old male with no family history of neurofibromatosis, initially presented with multiple café-au-lait macules on his extremities. Progressive blurry vision, predominantly in the left eye, developed subsequently. Ophthalmological examination revealed a cortical

cataract, a vertical flame-like ERM, CHRRPE, an astrocytic hamartoma, and an ONSM—all indicative of NF2[12-14]. Despite the absence of auditory symptoms, these NF2-specific ocular findings enabled an early diagnosis.

Several ocular findings of NF2 have been described in the literature, such as posterior subcapsular cataracts, wedge-shaped cortical cataracts, ERMs, and CHRRPE[13,15]. In adults, ERMs may be associated with various retinal diseases and may not be a primary indicator of NF2. However, in children, ERMs are an important diagnostic finding for NF2. Several studies have reported a characteristic pattern of unusual, flame-like ERMs extending to the vitreous in spectral-domain optical coherence tomography findings[16-18]. This pattern is consistent with the ocular manifestations observed in the present case. Importantly, recognition of ERMs in children may facilitate early diagnosis of NF2, even in neurologically asymptomatic individuals with a severe phenotype of NF2[19].

Furthermore, the present case shares similarities with a previously reported case of a 9-year-old boy who presented with CHRRPE, multiple presumed retinal astrocytic proliferations, and retinal astrocytic hamartomas[20]. These hamartomas, considered a type of glial tumor of the retinal nerve fiber layer, are typically associated with tuberous sclerosis[21]. However, retinal astrocytic hamartomas can also be incidental findings on retinal examination and are rarely reported in neurofibromatosis patients.

Several studies have established a relationship between retinal hamartomas, CHRRPE, and NF2. In some instances, retinal hamartomas have been reported as a leading sign preceding the development of vestibular schwannomas[22]. Similarly, a meta-analysis revealed that retinal hamartomas were observed before the clinical diagnosis of NF2 in 11 out of 25 cases[23]. These findings suggest that retinal hamartomas may be a clue for diagnosing NF2. Recently, ERMs in children have been proposed as a diagnostic criterion for NF2[19].

The progressive visual impairment in our reported case was caused by an ONSM compressing the left optic nerve. ONSMs are rare in pediatric patients, with an estimated prevalence of 1:95 000 to 1:525 000[24]. Vision loss, optic atrophy, and optociliary shunt vessels constitute the classic clinical triad of ONSMs. In the present case, the ONSM was located in the intraconal part of the left orbit, directly compressing the left optic nerve.

Evidence supporting the association between NF2 and ONSM is growing. Bosch et al. reported a strong association between ONSMs and NF2 in a case series of NF2 patients.[25] Their findings also suggest that there is an increasing awareness of the potential presence of NF2 in patients diagnosed with ONSM.

Strabismus, reported in 52% of NF2 patients, can manifest as either comitant strabismus (exotropia, esotropia, or mixed horizontal and vertical deviation) or as cranial nerve palsies affecting CN III, CN IV, or CN VI[26]. Our patient was diagnosed with exotropia and underwent bilateral lateral rectus recession. Strabismus has been documented in NF2 patients and may be the initial manifestation of NF2[11].

Children of NF2-affected parents are typically managed by NF2 specialists and undergo routine clinical screening and genetic testing, which facilitates timely diagnosis. In contrast, children without a family history of NF2 often face delayed diagnoses due to a lack of clinical awareness of initial symptoms. Children without vestibular schwannoma presentations have a mean diagnostic delay that is more than 12 months longer than that for children with a familial history of neurofibromatosis[3,12]. Presentations involving nonvestibular tumors in childhood may suggest more aggressive forms of neurofibromatosis[14,27]. Diagnosing NF2 at a young age can be particularly

challenging, leading to frequent diagnostic delays[28]. Younger patients often exhibit more ophthalmologic signs and symptoms than older patients. Thorough ophthalmologic examinations are crucial for diagnosing rare inherited diseases such as NF2. Early recognition of NF2-specific ocular findings may enhance awareness and facilitate prompt diagnosis in pediatric patients.

In summary, the ophthalmic findings of NF2 can be subtle, necessitating a dilated fundus examination to detect peripheral cortical cataracts, ERMs, and retinal hamartomas. Our case exhibited all NF2-specific ocular findings: cortical cataracts, ERMs, retinal hamartomas, and ONSMs. Such findings are critical for diagnosing NF2, particularly in early-onset cases. Spectral-domain optical coherence tomography can reveal the distinctive flame-like pattern of ERMs. Early diagnosis and appropriate management can reduce morbidity in NF2 patients and significantly enhance their survival rate.

Learning Points/Take Home Messages

• Neurofibromatosis type 2-specific ocular findings are crucial for diagnosing the condition in early-onset cases.

• In young children, optical coherence tomography effectively demonstrates the unique flame-like pattern of epiretinal membranes.

• Early diagnosis, optimal management, and a multidisciplinary team approach are essential for reducing morbidity and improving the survival of patients with neurofibromatosis type 2.

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อาการแสดงจำเพาะทางตาที่นำไปสู่การวินิจฉัยโรคท้าวแสนปมชนิดที่สองชนิดเกิดเร็ว

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บทคัดย่อ:

ภูมิหลัง: โรคท้าวแสนปมชนิดที่ 2 (Neurofibromatosis type 2 หรือ NF2) เป็นโรคทางพันธุกรรมที่พบได้น้อย ซึ่งมีลักษณะเด่นคือการเกิดเนื้องอกในระบบประสาทส่วนกลาง โดยเฉพาะเนื้องอกเส้นประสาท (Schwannoma) และเนื้องอกเยื่อหุ้มสมอง (Meningioma) การวินิจฉัยมักล่าช้าเนื่องจากอาการที่แสดงออกต่างกันไป ซึ่งอาการทางตาอาจเป็นอาการแสดงที่พบได้เร็วที่สุดในเด็ก

อาการและการดำเนินโรค: เด็กชายอายุ 4 ปี ถูกส่งตัวมาเพื่อตรวจตาเนื่องจากพบ café-au-lait macules หลายจุด ตรวจตาพบการมองเห็นลดลง ร่วมกับการ มี bilateral iris mammillation และ left retinal hamartoma ทำให้บ่งถึงโรค NF2 ผู้ป่วยได้รับแว่นตาเป็นการรักษาเบื้องต้น แต่ผู้ป่วยไม่ได้มาตรวจตามนัด เมื่อกลับมาตรวจซ้ำตอนอายุ 8 ปี พบว่าการมองเห็นในตาซ้ายมัวมากขึ้น ตรวจพบ flame-like epiretinal membrane (ERM) ในตาขวา และพบ combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) ในตาซ้าย Magnetic Resonance Imaging (MRI) ยืนยัน Schwannoma หลายจุด และ optic nerve sheath meningioma (ONSM) ที่ตาซ้าย และได้รับการวินิจฉัยว่าเป็น NF2 เมื่ออายุ 10 ปี

การอภิปราย: ผู้ป่วย NF2 ในเด็กมักมีอาการแสดงทางตาเกิดขึ้นก่อนอาการทางระบบประสาท เช่น cortical cataract , ERM, CHRRPE และ ONSMs การรู้จักอาการแสดงทางตาเหล่านี้ มีความสำคัญในการวินิจฉัยและจัดการโรคอย่างทันท่วงที ซึ่งอาจช่วยลดอัตราการทุพพลภาพทางการมองเห็นได้

สรุป: ในผู้ป่วยรายนี้ ได้แสดงถึงความสำคัญของการตรวจตาอย่างละเอียดของผู้ป่วย NF2 ในเด็ก การวินิจฉัยได้ตั้งแต่อายุยังน้อย จะสามารถนำไปสู่การรักษาที่เหมาะสมได้ในหลายสาขาวิชา และเป็นการเพิ่มโอกาสการรักษาผู้ป่วย NF2 ในเด็ก

คำสำคัญ: ฮามาร์โตมาของจอตา, จักษุวิทยาเด็ก, เนื้องอกของเยื่อหุ้มเส้นประสาทตา, โรคท้าวแสนปม, โรคท้าวแสนปมชนิดที่สอง

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