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Neurofibromatosis type 1–related hydrocephalus: causes and treatment considerations

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Abstract
The prevalence of hydrocephalus among patients with neurofibromatosis type I (NF1) is estimated to be between 1 and 13%. Most hydrocephalic causes are obstructive—aqueductal webs, chiasmatic-hypothalamic tumors, and thalamic mass effect related to NF changes. Other NF1-related conditions may mimic the clinical presentation of hydrocephalus and should be ruled out while evaluating children with headaches. These include brain tumors and moyamoya syndrome. Treatment of NF1-related hydrocephalus should be personally tailored, including tumor resection or debulking, shunts, and endoscopic procedures such as septostomy and third ventriculostomy. Despite these personalized treatments, many of the primary treatments (including shunts and endoscopic procedures) fail, and patients should be screened and followed accordingly. In the current manuscript, we review the causes of NF1-related hydrocephalus, as well as treatment options.

Keywords Neurofibromatosis 1 · Hydrocephalus · Optic pathway glioma · Endoscopic third ventriculostomy · Shunt

Introduction

Neurofibromatosis type 1 (NF1) is the most common neurocutaneous syndrome, caused by an inherited or spontaneous mutation in chromosome 17. The CNS manifestations of NF1 include tumors, such as optic pathway gliomas (OPGs), non-tumoral hamartomatous tissue changes (often classified as "NF changes"), spinal neurofibromas, and associated manifestations such as seizures and hydrocephalus [1]. About 17–30% of NF1 patients suffer from headaches, with most data originating from adult series [2, 3]. This prevalence is similar to headaches among the general population.

The incidence of hydrocephalus in NF1 patients is estimated to be between 1% in adults and 13% in children [3, 4]. The reason for the wide incidence range may be related to different NF1 populations, such as different age groups, and whether patients were followed by neurological centers or by neurosurgical centers.

In the following manuscript, we overview the various etiologies of NF1-associated hydrocephalus, as well as treatment options.

Etiology of NF1-associated hydrocephalus

NF1 patients are prone to develop obstructive hydrocephalus secondary to OPGs, other CNS tumors, NF changes with a mass effect compressing the CSF pathways, and aqueductal stenosis [4–11]. Causes such as an aqueductal web, periaqueductal gliosis, NF tissue changes, or tumors in the midbrain (including tegmental or tectal regions), or unilateral thalamic masses, all lead to triventricular obstructive hydrocephalus (Figs. 1, 2, and 3) [4–9, 11–14].

The actual pattern of hydrocephalus depends on the exact location of the obstruction. A large OPG, obstructing the third ventricle, may lead to obstruction of both foramina of Monro, leading to biventricular hydrocephalus (Fig. 4). A unilateral thalamic or basal ganglia mass may lead to obstruction of the body of the third ventricle and obstruction of the foramina of Monro, or may cause obstruction of the posterior third

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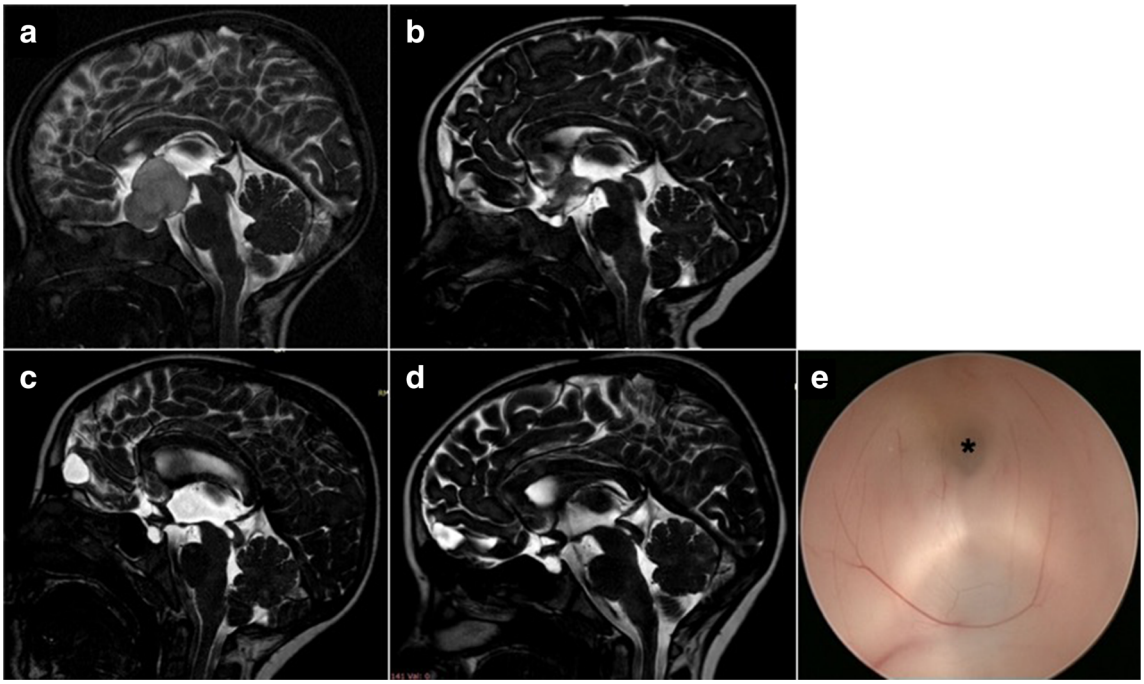

Fig. 1 **a** NF1 patient at the time of diagnosis of OPG at the age of 13 months. **b** The same patient at the age of 30 months, following completion of LGG chemotherapy. **c** At the age of 7 years, OPG is stable but hydrocephalus with aqueductal stenosis is evident. **d** Three months after ETV, hydrocephalus is resolved and CSF flow artifact is visible. **e** Intra-operative view of the third ventricular floor. The point of perforation is the most anterior attenuated membrane (asterisk). Difficult anatomy makes navigation mandatory

ventricle and aqueduct, leading to triventricular hydrocephalus (Fig. 5).

Prior surgeries for resection of upper cervical neurofibromas may lead to local scarring to the fourth ventricular outlet—leading to fourth ventricular outlet obstruction (FVOO), presenting with enlargement of all 4 ventricles. Prior surgery for other CNS-related pathologies may cause obstructive and non-obstructive hydrocephalus. Arachnoid

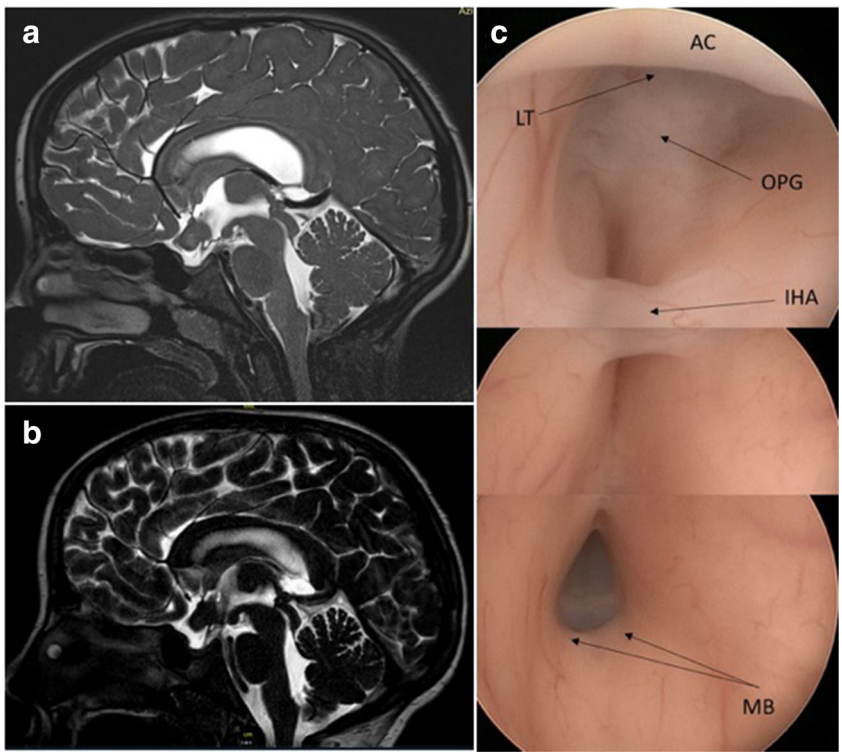

Fig. 2 A 6-year-old NF1 patient. **a** Routine follow-up MR allowed the diagnosis of hydrocephalus due to aqueductal stenosis of the proximal third and a small dorsally exophytic OPG. **b** MRI performed 24 h after ETV and endoscopic biopsy of the OPG. **c** Combined views of the floor of the patient. Anatomical views can be highly misleading in such a case. Tuber cinereum is the most posterior, attenuated membrane just ahead of the mammillary bodies (MB). Anteriorly an interhypothalamic adhesion is seen (IHA) and more anteriorly the optic pathway glioma (OPG), the small recess of the Lamina Terminalis (LT) below the Anterior Commissure (AC). Navigation was key for a correct orientation and anatomical interpretation

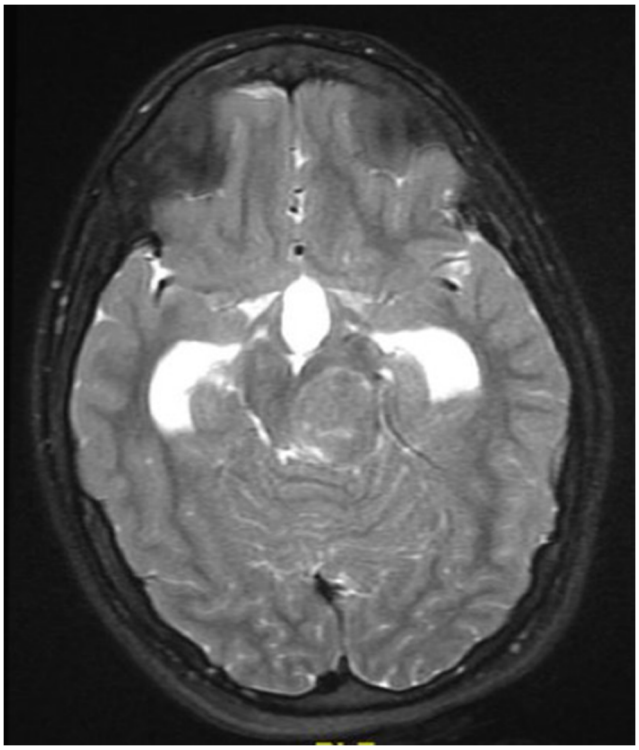

Fig. 3 A 13-year-old girl with a midbrain mass. Axial T2-weighted image. Underwent an ETV and followed for 7 years. The tumor mildly grew and was never treated

thickening may cause increased intracranial pressure [15]. Brainstem NF tissue changes may lead to obstructive hydrocephalus too (Fig. 6).

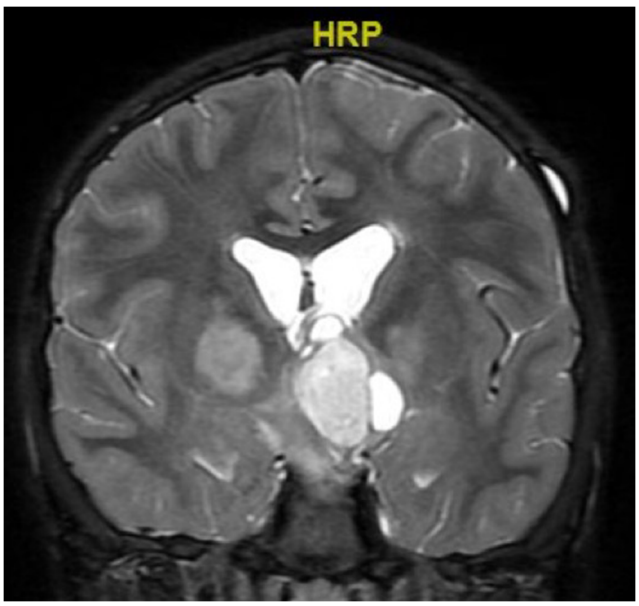

Fig. 4 A 10-year-old boy with a large OPG obstructing the foramina of Monro. Coronal T2-weighted images. The child underwent a septostomy and a shunt. Over the years, he underwent various chemotherapy treatments, and eventually a subtotal resection of the tumor (which was a pilocytic astrocytoma)

Thus, NF1-associated hydrocephalus is not a unified entity, but a multifactorial condition, with many etiologies leading to various types of hydrocephalus, most of which are obstructive in nature.

Symptoms of NF1-associated hydrocephalus

Similar to hydrocephalus caused by any other etiology, symptoms depend on acuity of hydrocephalus, age of patient, and comorbidities [11]. Additionally, symptoms and signs of increased intracranial pressure may overlap with other NF1-associated pathologies such as OPG, brain tumors, and moyamoya syndrome.

OPG in infants may present with diencephalic syndrome, accompanied by vomiting, even without the presence of hydrocephalus. Additionally, visual decline may be secondary to OPG, and not necessarily be related to hydrocephalus. However, a low threshold for imaging should be maintained for children with NF1 of all ages, to diagnose any associated pathology—be it OPG (or dynamics in a known OPG), moyamoya syndrome, other brain tumors, or hydrocephalus.

Diagnostic modalities of NF1-associated hydrocephalus

MRI is the modality of choice for evaluating headaches in children with NF1. Apart from diagnosing hydrocephalus and its causes, tissue changes associated with moyamoya should be sought for (such as ischemic insults and IVY sign changes), and MRA may be advised too in specific cases. Specific sequences including T2 SPACE, CINE, FIESTA, and other protocols enhancing obstruction in the aqueduct may be indicated, similarly to non-NF1 children presenting with hydrocephalus. Gadolinium contrast is indicated at least at the initial scan—to rule out tumors.

Spinal MRI is warranted in the presence of hydrocephalus with no obstructing culprit, to rule out a spinal tumor.

Treatment of NF1-associated hydrocephalus

Treatment of NF1-associated hydrocephalus may be focused specifically on the cause of hydrocephalus, or on the hydrocephalus itself.

NF1-related OPG may be treated with chemotherapy, and lately also BRAF or MEK inhibitors [16, 17]. The role of surgery in the treatment of NF1-related OPG is debatable, and reserved for extensive tumors leading to significant mass effect, or growing tumors despite medical treatments. OPG in NF1 may lead to hydrocephalus through several mechanisms. Local obstruction of basal cisterns will lead to enlargement of

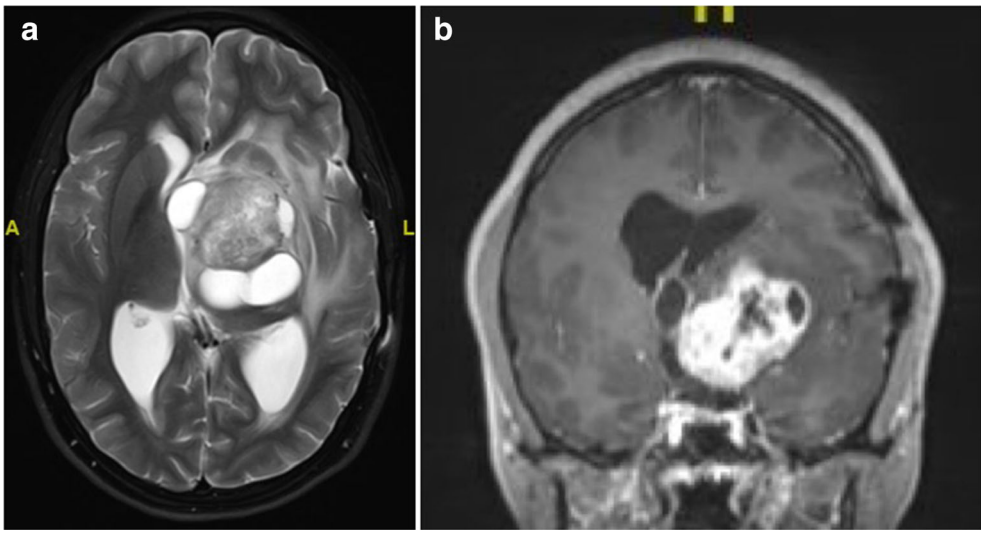

Fig. 5 A 16-year-old girl with a large basal-ganglia—thalamic tumor-causing obstruction of the foramina of Monro and compression of the third ventricle. **a** Axial T2-weighted and **b** coronal T1-weighted with contrast images. She underwent a subtotal resection (pathology was ganglioglioma grade I), followed by a shunt

all 4 ventricles. Obstruction of the third ventricle may lead in some cases to obstruction of the foramina of Monro, causing bilateral isolated hydrocephalus. These cases may be treated by tumor resection (even partial) [18]; however, a shunt may be an alternative option (coupled with a septostomy if the foramina of Monro are obstructed), followed by chemotherapy [10, 19–21]. Shunts for hydrocephalus associated with OPG have been associated with increased risk of ascites, probably related to the secretion of protein by the tumors [22]. Endoscopic treatments of OPG may include tumor biopsy, partial tumor debulking, and fenestration of tumor-related cysts [18, 23].

In cases with triventricular hydrocephalus, depending on the anatomy of the third ventricular floor and the presence of an OPG, an ETV is a valid treatment option. In a recent multinational study composed of 42 patients with NF1 that underwent an ETV, we found a success rate of 76% for selected patients with NF1-related hydrocephalus [6]. ETV may be performed for triventricular hydrocephalus even in the presence of an OPG, if the OPG does not involve the third ventricular floor. In selected cases, a trans-stoma stent may be recommended to maintain stoma patency [6, 24].

Thalamic NF-related tissue changes are usually bilateral and may compress the third ventricle, causing bilateral obstructive hydrocephalus with no obstruction of the Monro. Hydrocephalus caused by unilateral thalamic lesions is usually triventricular; however, as the compressing vector may compress the body of the third ventricle too, this may affect local anatomy and surgical considerations [25].

Other etiologies for hydrocephalus include posterior fossa or cranio-cervical compaction from tumors or NF-related hamartomas (NF changes), brainstem tumors, spinal tumors,

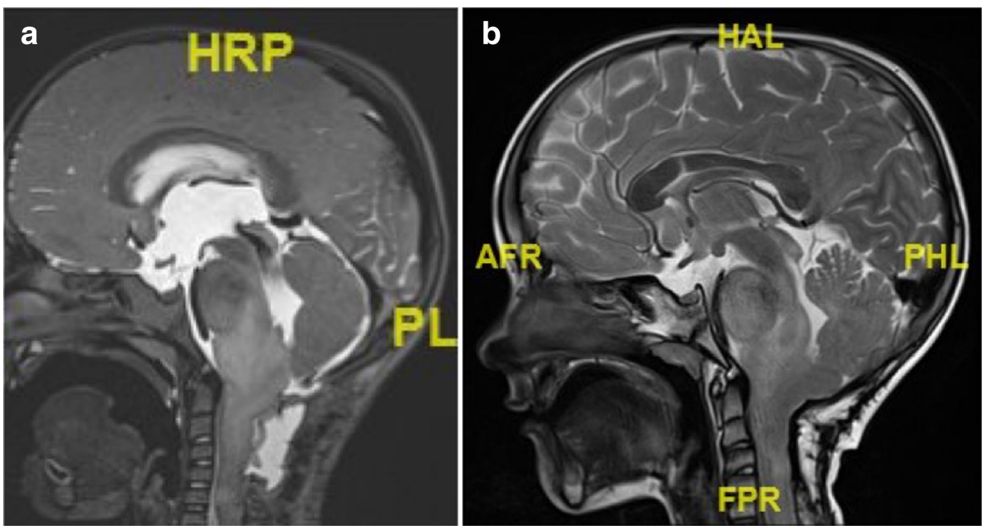

Fig. 6 A 4-year-old boy with extensive cervico-medullary tissue swelling and tissue changes. **a** Mid-sagittal T2-weighted image following an upper cervical laminectomy and duroplasty for reducing the upper cervical pressure. The child had secondary obstructive hydrocephalus. He underwent an ETV which failed over a course of a few weeks, followed by a shunt (**b**)

and postoperative conditions [26, 27]. Despite the obstructive nature of some of these conditions, ETV success rates are limited.

Despite the wide range of treatment options including endoscopy or shunts, often in combination (such as adding a septostomy, or inserting an Ommaya), our experience suggests a high failure rate (60–71%) for a primary treatment—either endoscopic or shunt procedures. Failure occurred in a bimodal pattern, either during the first 6 months after surgery or after at least 3 years [11]. Thus, patients and families should be educated to be aware of any new symptoms, and patients should be screened for early detection of treatment failure.

Currently, there is limited literature concerning treatment paradigms. The causes of hydrocephalus in NF1 may be multifactorial; thus, treatment is often multimodal, combining treating the CSF aspects, tumor resection, chemotherapy, and observation. Even after successful CSF treatment, the primary etiology may continue to evolve, potentially affecting the long-term outcome.

Conclusion

Hydrocephalus in the context of NF1 is caused mostly by *obstructive* etiologies. A tailored treatment approach, addressing the specific etiology, is recommended. Regardless of the treatment approaches, a high rate of failures is described.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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