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REVIEW ARTICLE

Pathogenesis of hydrocephalus in achondroplastic dwarfs: a review and presentation of a case followed for 22 years

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Abstract

Object The purpose of this work is to review the pathogenesis and pathophysiology of hydrocephalus in patients with achondroplasia as a guide to its management throughout life.

Methods A review of the literature related to neurosurgical issues in achondroplasia with specific focus on cerebrospinal fluid physics, clinical management, and outcome of affected individuals. Issues involved in this review are highlighted by a case report of a patient shunted for achondroplasia first shunted in infancy and followed for 22 years. Each of the management issues is explored with respect to this patient.

Findings Head circumferences in achondroplasia are abnormally large in this condition usually caused by excess cerebrospinal fluid in the cortical subarachnoid space. Increase in ventricular size (hydrocephalus) is not rare but should not be treated unless rapidly progressive or symptomatic. The underlying cause of the abnormalities of cerebrospinal fluid dynamics relates to abnormal venous drainage at the skull base. Patients shunted in infancy for hydrocephalus usually remain dependent on the shunt for life, and crises of high intracranial pressure may occur with no distention of the ventricles.

Conclusions In infants with achondroplasia, large heads and enlarged ventricles without symptoms should be watched initially for progression. If hydrocephalus progresses or if symptoms of intracranial hypertension occur, endoscopic third ventriculostomy can be tried. If shunt is necessary, it should have a high opening pressure and a device to retard siphoning. In the case of recurrent ventricular catheter blockage, it may be necessary to create a communication between the ventricles and the cortical subarachnoid space.

Keywords Hydrocephalus · Achondroplastic dwarfs · Endoscopic third ventriculostomy · Slit ventricle syndrome

Introduction

Hydrocephalus is a relatively common feature in children with achondroplasia occurring in 15–50% of patients [1, 2]. The pathogenesis of hydrocephalus in this context has been studied thoroughly and has been found to relate to increased pressure in the dural venous sinuses due to constriction of venous drainage both at the level of the jugular foramina and stenosis of the foramen magnum in these children [2–6]. Macrocephaly is an established clinical hallmark for achondroplasia as well as the facial features related to the development of the skull base. For the majority of dwarfs, this macrocephaly relates to an excessive volume of cerebrospinal fluid in the cortical subarachnoid space (CSAS), but ventriculomegaly (hydrocephalus) can also be present. In more severe cases, triventricular hydrocephalus due to closure of the aqueduct may occur as a secondary phenomenon [7, 8]. Secondary closure of the aqueduct was first described by Nugent et al. who suggested that this occurs as a result of the distension of the temporal horns of the lateral ventricles and downward distortion of the third ventricle [9].

The cause of hydrocephalus in achondroplastic dwarfs is not a problem of brain development but relates to the formation and growth of the skull. The underlying cause of the condition relates to mutations of the FGFR3 gene leading to maldevelopment of the skull base that has been preformed in cartilage [10]. The skull is made up of both enchondral bone of the skull base and membranous bone of the remainder of the calvarium. The membranous bone has no genetically determined shape or size. It is derived from the dura mater, and

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its shape and size are dependent on the distension of the dural covering due to the growth of the brain and increase in the reservoirs of cerebrospinal fluid (CSF). Moss in his studies of skull growth and distortion has named the dura in this context as the "neurocranial capsule" [11]. The skull base including the basiocciput, the sphenoid, and the petrous portions of the temporal bone has a genetically determined size and shape and is preformed in cartilage. It is therefore called enchondral bone. In achondroplasia, these structures are hypoplastic and multiple synchondroses linking these bones are fused prematurely. The outcome of the abnormal development of the enchondral skull is that the skull base is small leading to stenosis of the jugular foramina and the foramen magnum. The growing brain is of proper size but is distorted by the small volume of the inferior areas of the cranium.

The abnormalities in the skull base lead to compression of the central nervous system at the cervicomedullary junction and may result in a small or absent cisterna magna. The stenosis of the jugular foramina may impede the flow of venous blood both to the jugular vein and through the veins draining through the foramen magnum. In achondroplastic dwarves with hydrocephalus, measurement of the pressure in the jugular veins shows a pressure gradient at the level of the jugular foramen and high pressures in the dural venous sinuses [1, 2]. Hydrocephalus results from a failure of flow of CSF from its point of formation within the ventricles to its final reabsorption into the systemic circulation. If venous hypertension develops in a patient in whom the sutures and fontanels have solidified, the patient develops severely increased intracranial pressure but does not develop hydrocephalus [12]. If on the other hand the skull can enlarge, such as the infant with open sutures, venous hypertension results in increases in the amount of CSF within the calvarium primarily in the cortical subarachnoid space and may result in a unique form of hydrocephalus with communication between the ventricles and the CSAS. Dwarfs with hydrocephalus can be shown to have excess CSF both within the ventricles and in the cortical subarachnoid space.

A great deal of research is now showing that there are multiple sources of CSF absorption. Classically, it has been assumed that CSF is absorbed into the dural venous sinuses via arachnoid villi or granulations. It is clear that the answers are much more complicated and there are multiple sources of CSF absorption including the cribriform plate, following cranial and spinal nerve exits, lymphatics, and direct absorption of the CSF into parenchymal vasculature [13, 14]. Infusion studies and ICP monitoring do document a pressure gradient between the cortical subarachnoid space, and these sinuses show that absorption of CSF relates to a gradient of pressure from the CSAS to the dural sinuses as if the absorption was into these sinuses [15].

Support for the hypothesis that hydrocephalus in achondroplasia is due to venous hypertension derives from multiple sources. These patients will show increased numbers and diameters of emissary veins [3]. Significant pressure gradients have been documented across the stenosed jugular foramina [1, 2]. Successful treatment of the hydrocephalus has been reported with the use of transverse sinus to jugular vein bypass and surgical decompression of the jugular foramen [4–6]. It is important to recognize that hydrocephalus in this situation results not from malformation of the central nervous system but from disruption of flow of venous blood and therefore buildup of excess CSF leading to the macrocephaly and in severe cases to hydrocephalus. The intellectual outcome in achondroplastic patients is likely normal [16].

Macrocephaly in achondroplasia is part of the phenotype of the condition, and a large head and short limbs are expected. Head circumference charts for achondroplastic children show head growth to be greater than a normal population. Early rapid head growth with increase in CSF in the CSAS is to be expected [17–20].

Exemplary case report: story of a 22-year-old woman shunted in infancy for hydrocephalus in the context of achondroplasia

Initial presentation At 3 months of age, she presented to her pediatrician with severe irritability and a rapidly growing head with a bulging fontanel. MRI performed at that time revealed significant ventriculomegaly but also showed prominent CSF in the cortical subarachnoid space (Fig. 1). A week later, she underwent a ventriculoperitoneal shunt with resolution of the symptoms (Fig. 2). During that hospitalization, she was found to have achondroplasia.

First shunt failure At 15 months, she presented with shunt failure with the shunted ventricle having collapsed around the ventricular catheter and the contralateral ventricle being of normal size and the septum pellucidum bowed to the side of the catheter (Fig. 3). At this point, the shunt was revised with clearing of the ventricular catheter and upgrading the valve. This procedure was complicated by a shunt infection requiring removal and replacement of the shunt system and antibiotics. The shunt system at this point related to an adjustable valve system with a device to retard siphoning. At this point, she was being treated for "slit ventricle syndrome."

Second episode of shunt failure Approximately a year later, she presented acutely ill with lethargy, vomiting, and severe headaches. Again, the ventricular catheter had failed due to collapse of the ventricle. Treatment at this point included the placement of a ventricular catheter into the cortical subarachnoid space to balance the pressure within the lateral ventricle with that in the cortical subarachnoid space. A total of nine shunt revisions were required over the next 16 months. Following this epoch, she required no neurosurgical

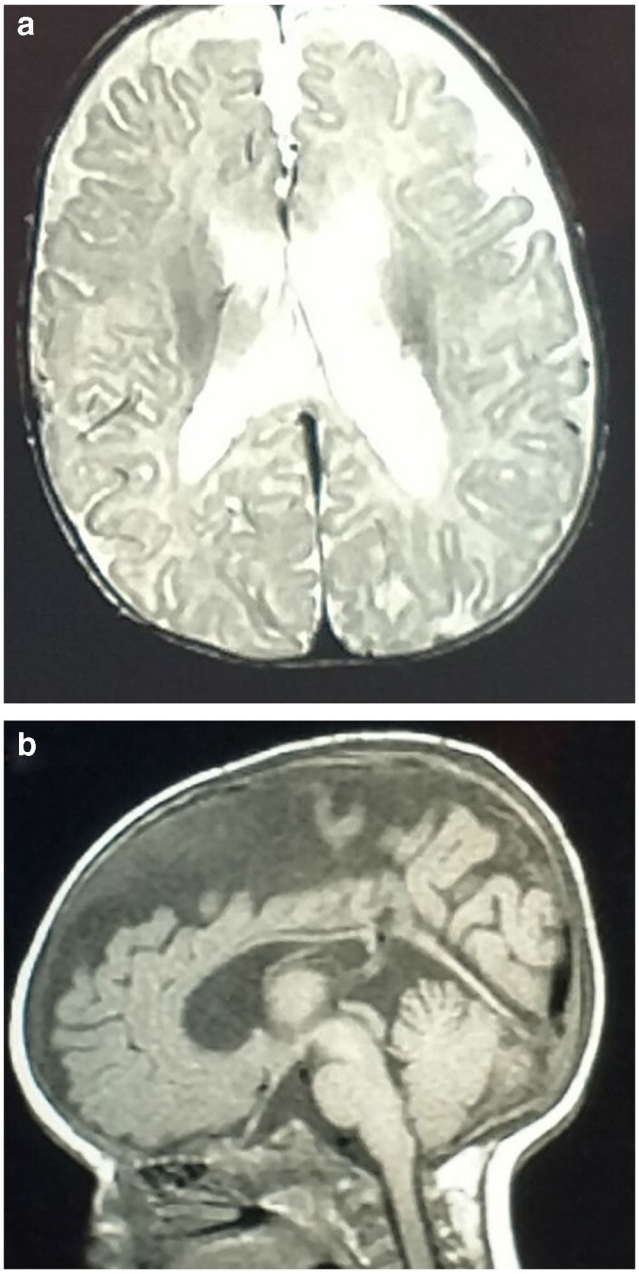

Fig. 1 **a** Axial T2 MRI image from MRI prior to the first shunt surgery showing both increase in ventricular size and increase in CSF in the cortical subarachnoid space. **b** Sagittal T1 image preoperatively also showing markedly increased subarachnoid CSF

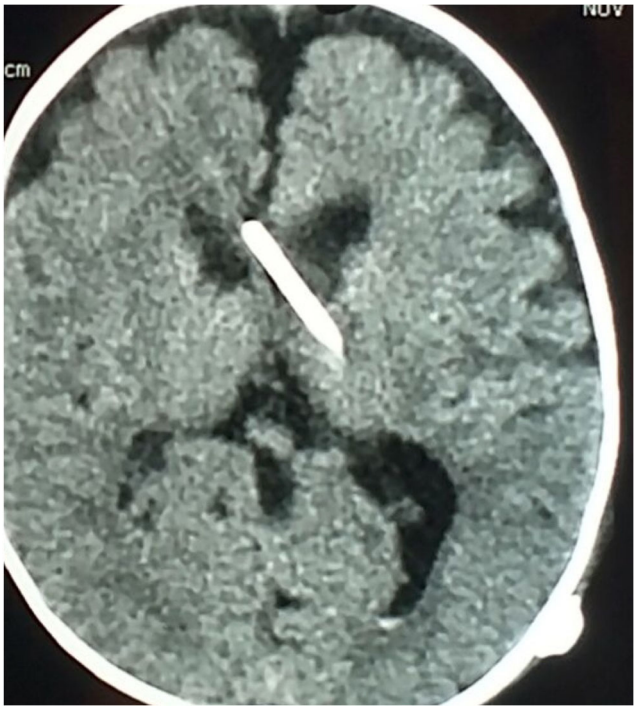

Fig. 2 CT scan of brain the day after the first shunt surgery showing decrease in both ventricular and subarachnoid CSF

intervention for the next 18 years. There was an episode at the age of 9 in which she was found to have enlarged ventricles bilaterally. A diagnostic procedure involving injection of iodinated dye into the ventricle through the shunt showed flow of the dye into the ventricle and then into the basal cisterns (Fig. 4) and ventricular enlargement. This is the only time since infancy in which the ventricles were found to be enlarged. This resolved without surgical intervention, and the ventricles returned to their slit-like condition. The assessment here was that the ventricular catheter had functionally failed, and the catheter in the cortical subarachnoid space had continued to function with selective drainage of the cortical subarachnoid space.

Adolescence and adulthood Beginning at the age of 12, she developed a severe headache disorder occasionally associated with myoclonic seizures treated for migraine. At the age of 21, she was seen in the emergency room twice in 1 week suffering from debilitating headaches, vomiting, and pain along the shunt tract. Following multiple attempts to manage the headaches including migraine medications and multiple changing of the valve pressure, she underwent a revision of the shunt and the valve was replaced. Postoperatively, she was actually worse with diplopia (sixth nerve palsy). Subsequently, she was found to have a shunt infection requiring a removal of the entire shunt system and antibiotic treatment with an external drainage system. On replacement of the shunt, a ventriculoperitoneal shunt with a single ventricular catheter was inserted. Intracranial pressure (ICP) measurements consistently showed elevated pressures with recordings varying from 40 to 75 mmHg. At this point, she showed signs of optic nerve damage and hearing loss. At this point, she underwent the placement of a cortical subarachnoid space catheter and connecting it to the existing ventricular catheter above the valve. This procedure led to balancing of ICP between the ventricle and the CSAS. She is now home with minimal headache and improvement in hearing loss as well as the visual difficulties of diplopia and blurred vision.

Assessment and treatment of infants with achondroplasia and hydrocephalus

The decision as to whether or not to intervene when faced with the diagnosis of hydrocephalus and abnormal head growth is made in an infant with achondroplasia will have significant consequences for the entire life of the patient. In an important article titled "Neurosurgical implications of achondroplasia" by King and colleagues from the Hospital for Sick Children in Toronto, 29 children with achondroplasia who required neurosurgical care were evaluated between 1956 and 2009. In this study, 12 patients were shunted requiring 52 shunt surgeries (4.3 surgeries per patient). As of 1990, a decision was made to accept a larger head and larger ventricles, and since that time, only one new patient has undergone shunting for hydrocephalus secondary to achondroplasia [10].

Hydrocephalus may be defined as "An active distension of the ventricular system of the brain related to inadequate passage of CSF from its point of production within the ventricular system of the brain to its point of absorption into the systemic circulation" [21, 22]. In babies in whom the fontanels and sutures remain open, the skull grows with increases in CSF in the CSAS. If sufficiently severe, the backup of CSF can lead to ventriculomegaly (hydrocephalus). Venous hypertension not only causes a distal CSF absorption problem but also leads to an increase in the stiffness or turgor of the brain. This increased turgor remains even when the intracranial pressure is lowered with shunting.

Performing a ventriculoperitoneal shunt in the setting creates a transmantle pressure gradient with the pressure in the cortical subarachnoid space higher than that within the ventricle. Unless the opening pressure of the valve is equal to or greater than the pressure in the CSAS, this fluid reservoir increases at the expense of the CSF in the ventricles which leads to anatomic slit-like ventricles. The ventricular walls collapse around the ventricular catheter and cause obstruction to flow. There is no CSF around the catheter so even though the ICP is now greater than the opening pressure of the valve, this does not always open the shunt to flow. In such a situation, the first step would be to surgically clear the ventricular catheter so that CSF can flow through it and make certain that the pressure within the ventricle is high enough to overcome the transmantle pressure gradient. This strategy involves the use of a valve with a very high opening pressure and the use of a device to prevent siphoning of which there are multiple designs.

The first surgical decision

The brain itself should be assumed to be normal in its development, and essentially, all babies with achondroplasia have large heads. As stated above, usually macrocephaly relates to excessive CSF in the cortical subarachnoid space around the brain. In a large minority of achondroplastic babies, dilatation of the ventricles occurs and hydrocephalus is diagnosed. Decisions as to what to do at this time are critical. As stated in the King article above, most of these babies should be watched and intervention should occur only in the situation of clear danger to the baby [10]. This approach can also be supported by the recent work of Kulkarni and colleagues whose study regarding developmental outcomes of babies with hydrocephalus from infection undergoing shunt vs endoscopic third ventriculostomy (ETV) and coagulation of the choroid plexus showed that it was the volume of the brain and not the volume of the ventricles which determined outcome [23].

The lifetime risk of shunt failure is very high in this population, and there should be very clear evidence that the shunt is needed. Long-standing increase in intracranial pressure can lead to visual difficulties, and if watchful waiting is the choice, the continued assessment of vision in the infants and children would be necessary [24]. The patient discussed here as the exemplary case report showed clear signs of increased intracranial pressure, and it would have been difficult to fail to treat the hydrocephalus in this case.

Are there alternatives to ventricular shunting in the case of achondroplasia? As discussed above, hydrocephalus in achondroplasia develops with terminal failure of outflow of CSF into the systemic circulation, and therefore, the ventricular CSF flows to (communicates with) the CSAS. The purpose of ETV would be to allow CSF to flow from the ventricle to the CSAS and basal cisterns. Treatment by endoscopic third ventriculostomy would not make sense if this flow is unimpeded. The anatomy of the tentorium and the posterior fossa is quite abnormal and compressed. Abnormalities of the skull base with compression of the craniocervical region can lead to secondary restriction of flow either through the aqueduct of Sylvius or failure of flow into the CSAS at the skull base [9]. ETV in this population has been shown to lead to successful outcomes and has resulted in shunt independent arrest of hydrocephalus in these babies [7, 8]. It should be noted however that the anatomy of the floor of the third ventricle can be distorted and sometimes the performance on ETV can be difficult [8].

Hydrocephalus in dwarfs is due to high dural venous sinus pressures primarily related to stenosis of the jugular foramina as discussed above. This concept is supported by the early work of Sainte-Rose and colleagues who successfully treated three cases of hydrocephalus in dwarfs by the use of a transverse sinus to jugular vein bypass [5, 6]. More recently, Lundar and colleagues have reported successful management with decompression of the jugular foramen [4]. These techniques deal with the underlying cause of the hydrocephalus and are very interesting, but more experience is necessary before these techniques can be recommended.

Severe slit ventricle syndrome in achondroplasia

The term slit ventricle syndrome (SVS) relates to severe headache disorders in chronically shunted individuals without ventriculomegaly. The diagnosis of the cause of the headaches cannot be assessed simply on imaging. Based on invasive monitoring of ICP 5, distinct clinical syndrome may be characterized as due to SVS [25].

1. Extreme low-pressure hydrocephalus analogous to spinal headaches.
2. Intermittent proximal obstruction of the ventricular catheter.
3. Shunt failure with ventricles that do not expand called "normal volume hydrocephalus" (NVH).
4. Intracranial hypertension in patients with a working shunt.
5. Headaches in chronically shunted hydrocephalus not related to intracranial hypertension.

An accurate diagnosis of the cause of the headache is important for the development of a management plan. Excessive drainage of ventricular CSF is common to all, and for the most part, the key feature would be to make certain that the opening pressure of the valve mechanism is sufficiently high to prevent this over-drainage and that shunt contains a function that prevents extreme low pressures when the patient is erect generically referred to as a "device to retard siphoning" (DVS). In the case of chronic headaches in all five sets of patients, the first step would be to upgrade the shunt system to decrease the inward pressure within the ventricles related to the cortical subarachnoid space [26].

As stated above, the pathogenesis of hydrocephalus in achondroplasia relates to increases in pressure in the dural venous sinuses leading to increases in the volume of the CSAS and increase in the turgor of the brain itself. Overall, in patients shunted in infancy, the likelihood that the ventricles will not expand at the time of shunt failure was found in one unselected study that was 9% [27]. While specific data are not available, it is very likely that NVH is a prevalent issue in the achondroplastic dwarf with a shunt.

The pathophysiology of severe SVS remains somewhat controversial. Patients shunted in infancy are likely to have a very thick calvarium and may show signs of early fusion of the sutures leading to the assumption that the problem relates to decrease in intracranial volume, and therefore, the increase in ICP may be due to cephalocranial disproportion [28, 29]. One approach to this problem therefore has been to perform an operation which increases the volume within the skull. This procedure which increases to total volume available for expansion of the CSF compartment both within and outside the ventricle will improve compliance and has been shown in some patients to improve the clinical condition [30]. The performance of a cranial expansion using a bi-coronal or bi-mastoid incision can lead to poor skin healing in patients who have complex problems related to hydrocephalus and may require subsequent shunt revisions and possible difficulty with wound healing in these patients.

Management of SVS in general and NVH that are refractory to manipulation of the ventricular shunt are managed with shunt systems that accesses the cortical subarachnoid space as well as the ventricles thus preventing the development of a transmantle pressure differential where the pressure in the CSAS is greater than that in the ventricle. For most patients, this goal is best obtained by a lumboperitoneal shunt in patients whose ventricular CSF can be accessed via the lumbar theca [31, 32]. This technique will drain both the ventricles and the CSAS and prevents the development of a pressure gradient.

Unfortunately, one of the problems facing patients with achondroplasia is the severe degree of spinal stenosis that they have which precludes the use of lumbar shunting in most cases. The goal of management of NVH should be to balance the pressure in the ventricles with that in the cortical subarachnoid space. In patients whose ventricles expand, this can be accomplished by performing an ETV. The goal is accomplished by the use of the placement of a catheter in the cisterna magna or in the CSAS directly. This catheter should be spliced into the shunt system in communication with the ventricular catheter above the valve [33, 34].

If a complex shunt such as described here is needed, it is essential that patient or the family understand fully why this has been done and documentation supplied to explain the vital function of the second catheter to subsequent neurosurgical care.

Distension of the ventricles

In NVH, the ventricles remain small despite shunt failure and extremely high ICP. Some have theorized that chronic shunting leads to irrevocable changes in the brain that prevent the ventricles from expanding [30, 35]. Insight into this controversy is illuminated by an episode in the long history of the exemplary patient described above. At 1 year of age, she underwent placement of a CSAS to ventricle to peritoneal shunt which worked well with a normal life until an episode at the age of 8 when she presented with a probable shunt obstruction and underwent an injection of iohexal dye to determine the functioning of the two arms of the complex shunt. At that time, she was found to have significantly enlarged ventricles (Figs. 3 and 4). This study showed that the ventricles were accessed as were the basal cisterns. Following the study, her symptoms resolved and the ventricles returned to their previous slit-like condition. She remained asymptomatic for the next 11 years. As stated in the case report at the time of

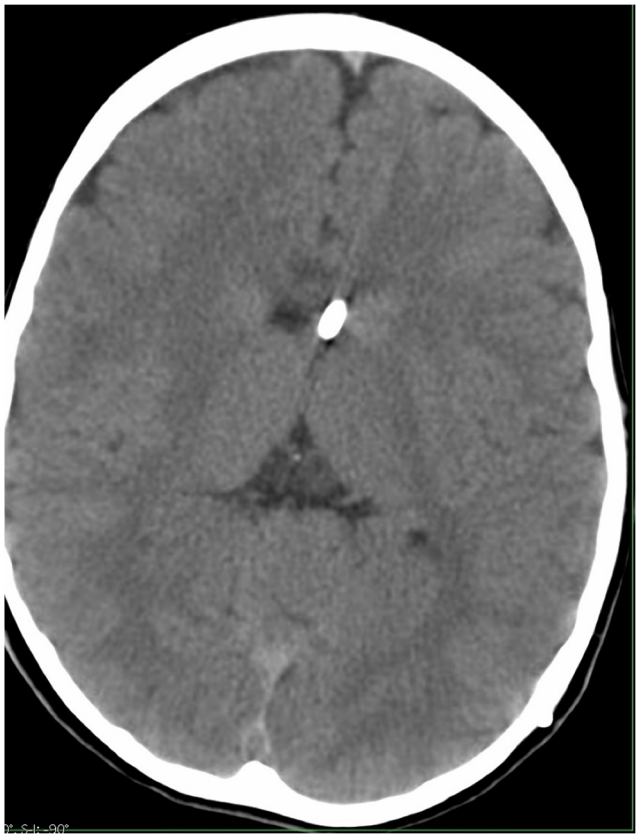

Fig. 3 CT scan of brain showing subnormal volume of the ventricles with collapse of the ventricle blocking the ventricular catheter typical of all but one scan after age of 2 years

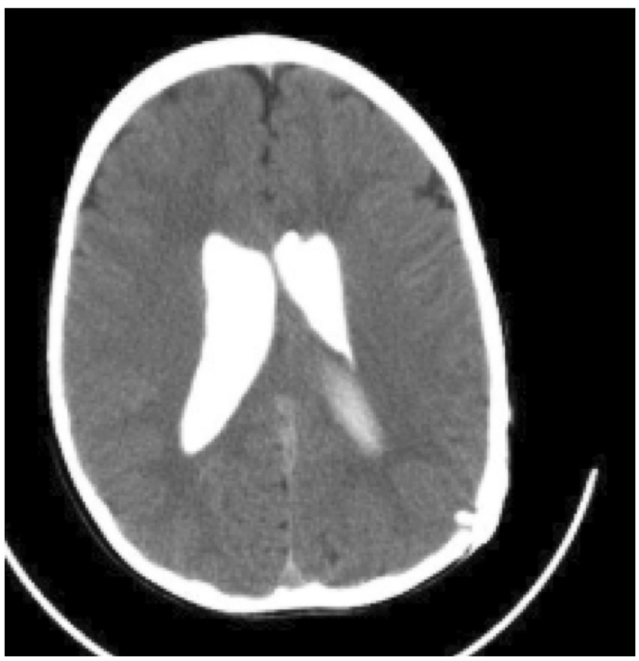

Fig. 4 CT study dye study showing enlargement of the ventricles at a time when the ventricular catheter failed but the catheter in the cortical subarachnoid space continuing to function selectively draining the cortical subarachnoid space

shunt failure from fracture of the valve mechanism, she was found to have slit-like ventricles with high ICP and very small ventricles.

Assessment of this event leads to a conclusion that at the time of presentation at age 8, she had a failure of the ventricular catheter with continuing functioning of the arm in the cortical subarachnoid space leading to a transmural pressure difference with the pressure in the ventricle being higher than the low pressure in the CSAS. This is the same pathophysiology seen in "negative or unexpectedly low" pressure hydrocephalus [36, 37]. In this rare condition, it has been shown that there is a failure of flow between the ventricles and the CSAS and the ventricles with selective drainage of the CSAS. The transmantle pressure differential leads then to ventricular distention despite low or negative intracranial pressure. At least in this one, patient chronic shunting did not lead to changes in the brain itself to explain the failure of expansion but rather a reversal of the transmantle pressure difference as seen in patients with negative pressure hydrocephalus [37].

Conclusions

Patients with achondroplasia who are shunted in infancy remain shunt dependent for life and may have failure of the shunt mechanism into adulthood. It is essential to understand the specific physics of hydrocephalus in this condition in order to respond properly to late shunt failure. All of the issues related to this condition are demonstrated by the case of the exemplary patient described above. The review both of the patient and of newly acquired knowledge of the condition leads to these conclusions.

1. In infants with achondroplasia who present with a large head and ventriculomegaly, a period of "watchful waiting" and follow-up is likely to lead to a good outcome with normal cognition.
2. In babies with achondroplasia and progressive hydrocephalus consider third ventriculostomy.
3. If a shunt is needed, it must contain a high-pressure valve setting and a device to prevent significant siphoning.
4. In the case of recurrent proximal shunt failure, it is necessary to perform a shunt that can access the cortical subarachnoid space such as a cisterna magna to ventricle to peritoneal shunt with the splice proximal to the valve.

Compliance with ethical standards

Conflict of interest I the author of this review attest that I have no conflicts of interest related to any aspect of the paper.

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