Spontaneous intracranial hypotension secondary to congenital spinal dural ectasia and genetic mosaicism for tetrasomy 10p: illustrative case

Peyton L. Nisson, MD,1 Rhona Schreck, PhD,2 John M. Graham, Jr., MD, ScD,3 Marcel M. Maya, MD,4 and Wouter I. Schievink, MD1

1Department of Neurosurgery, 2Department of Pathology, 3Medical Genetics, Department of Pediatrics, and 4Department of Radiology, Cedars-Sinai Medical Center, Los Angeles, California

BACKGROUND  Spontaneous intracranial hypotension has historically been a poorly understood pathology that is often unrecognized and undertreated. Even more rarely has it been described in pediatric patients with an otherwise benign past medical history.

OBSERVATIONS  Herein the authors describe one of the youngest patients ever reported, a 2-year-old girl who developed severe headaches, nausea, and vomiting and experienced headache relief after lying down. Imaging revealed tonsillar herniation 14 mm below the foramen magnum, presumed to be a Chiari malformation, along with extensive dural cysts starting from thoracic level T2 down to the sacrum. She was found to have streaky skin pigmentary variation starting from the trunk down to her feet. Genetic analysis of skin biopsies revealed mosaicism for an isodicentric marker chromosome (10p15.3–10q11.2 tetrasomy) in 27%–50% of cells. After undergoing a suboccipital and cervical decompression at an outside institution, she continued to be symptomatic. She was referred to the authors' hospital, where she was diagnosed with spontaneous intracranial hypotension.

LESSONS  After receiving a series of epidural blood patches, the patient experienced almost complete relief of her symptoms. To the authors' knowledge, this is the first time this chromosomal anomaly has ever been reported in a living child, and this may represent a new genetic association with dural ectasia.

https://thejns.org/doi/abs/10.3171/CASE213

KEYWORDS  intracranial hypotension; genetic mosaicism; tetrasomy 10p; dural ectasia; epidural blood patch

Once considered extremely rare, spontaneous intracranial hypotension (SIH) represents a poorly recognized disease entity that has recently been diagnosed with increasing frequency. The estimated incidence of 5 in 100,000 is likely an underestimate of the true rate.1 The expansion of magnetic resonance imaging (MRI) and awareness within the medical field of this pathology have led to a growing body of literature on this topic. Often patients are misdiagnosed with ailments such as migraine, tension headache, meningitis, transient ischemic attack, and psychogenic disorder before SIH is diagnosed.2 However, in some cases, symptoms can be progressive, eventually becoming debilitating and even life threatening.3,4

The most common cause of SIH is spinal cerebrospinal fluid (CSF) leak. Patients who are symptomatic classically have positional, orthostatic headaches; however, other symptoms can also develop, including neck pain, nausea, vomiting, vision changes, photophobia, and cognitive abnormalities, to name a few. SIH typically affects patients in the fifth and sixth decades of life, with a mean age of 40 years, and it has also been associated with a spectrum of connective tissue disorders, especially in the pediatric population.1,5,6 Only case reports and one case series have been published describing this disease in pediatric patients.6-8 Mosaicism for 10p tetrasomy was also identified in the child in the present case, a rare event reported only in a prior fetal report.9 We describe the first living patient, to our knowledge, with this genetic variant who had SIH.

Illustrative Case  The patient was a healthy female born at 38 weeks of gestation via repeat cesarean section, weighing 7 pounds, 1 ounce. She was an otherwise healthy child with normal growth and development. At age 2 years, she began complaining of severe headaches, screaming, “My

ABBREVIATIONS  CSF = cerebrospinal fluid; EBP = epidural blood patch; MRI = magnetic resonance imaging; SIH = spontaneous intracranial hypotension.

INCLUDE WHEN CITING  Published August 16, 2021; DOI: 10.3171/CASE213
SUBMITTED  January 2, 2021. ACCEPTED  June 14, 2021.
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head is on fire,” along with light and noise sensitivity, nausea, and vomiting. Her parents noticed that she would experience relief from her headaches after lying down. She was eventually taken to a nearby children’s hospital, where MRI of the brain revealed low-lying cerebellar tonsils 14 mm below the foramen magnum (Fig. 1A). There was no pachymeningeal enhancement on post-gadolinium T1-weighted MRI (Fig. 1B). When evaluating her for a cervical syrinx, multiple cysts and dilations of the dura were also found along the spine, extending down to the sacrum, as shown in Fig. 1C and D. Diagnosed with a Chiari 1 malformation at the outside facility, the patient underwent decompression with dural opening along with a thoracic laminectomy at T5 with biopsy of an epidural mass. The final pathology revealed normal but thinly dilated dura and venous tissue.

After the operation, she experienced improvement of her headaches, but they soon recurred with increasing frequency, accompanied by new onset of double vision. Episodes of bowel and bladder function loss, worsening hypersomnolence, chest tightness, and pressure in her left index finger also developed. Over the next 2 years, she was seen by multiple specialists in several tertiary and quaternary medical centers across the country. It was not until the age of 4 years and 8 months that she was referred to our center for further evaluation of CSF leak.

On examination, the patient was neurologically intact but was found to have hypopigmented streaks starting from her midthoracic region, going down her legs, with the left leg more affected than
the right. Consistent with hypomelanosis of Ito, this prompted a referral for a genetic work-up (Fig. 2). Per the patient’s family, these streaks had been present since birth, becoming more prominent after she spent time in the sun.

The results of outside evaluations at age 2 years by karyotype analysis and chromosomal microarray were reported to be normal in peripheral blood. Sequencing of some of the most common genes causing dural ectasia, including FNB1, TGFBR1, TGFBR2, and COL5A2, did not reveal any pathogenic variants. The following laboratory values were all within normal limits with some slight elevations but none consistent with a genetic disease: lactate, ammonia, urine organic acids, and serum amino acids. Repeat studies at age 4 confirmed a normal blood karyotype, 46,XX. However, karyotype analysis of skin biopsies from differently pigmented areas showed two populations of cells, with one having only normal 46,XX cells and the other (50%) having 47 chromosomes due to the presence of a supernumerary, medium-sized, metacentric marker chromosome (47,XX,+mar), as shown in Fig. 3. Chromosomal microarray analysis of the skin identified this marker chromosome as an isodicentric chromosome 10 [arr 10p15.3q11.22(135,655–47,688,677)x2 ~ 4] present in 27%–50% of cells from various samples from the hypopigmented regions. Thus, the abnormal cells were tetrasomic for all of the short arm of chromosome 10.

The patient underwent a 10-mL epidural blood patch (EBP) at the thoracic T11–12 level under anesthesia with somatosensory evoked potential monitoring. This level was chosen to allow the maximum amount of blood patching at an anatomically accessible and more capacious epidural space.

After this procedure, she experienced complete resolution of her headaches and no longer complained of double vision. For a total of 4 days, she experienced complete relief, but her symptoms recurred. After 1 month, they had all returned, but with lesser intensity, now with transient episodes of lower extremity weakness after a bowel movement, along with a sensation of pins and needles.

Four months after the first EBP, a second one was administered using the same technique. For the next 5 years, the patient experienced a relatively normal life with no missed school days, and she was fully active until she began to have some recurrence of hypersomnolence and worsening headaches. Interval computed topography myelograms and MRI myelograms were all stable between this time period (age 2 to 7 years). A third EBP was administered at this time. At the most recent 2-year follow-up since then, she reported complete resolution of her symptoms with the exception of occasional mild headaches.

**Discussion**

**Observations**

This case represents one of the youngest patients ever reported with SIH, second to a 1-year-old reported by Adler et al. in 2011.6,10–18 Despite being evaluated by several specialists spanning multiple tertiary and quaternary medical centers, 2 years elapsed before this patient was correctly diagnosed. Unfortunately, this experience is not unique or an outlier, as historically, the majority of patients with SIH have a delayed diagnosis.2 Despite the vast symptom overlap with other disease states, the presence of positionality in the history should always raise SIH on the differential diagnosis for clinicians. In this case, we recognized the extensive dural ectasia in the setting of orthostatic headaches as clear evidence of the patient’s intracranial hypotension. Although spine surgery and traumatic injury are well recognized risk factors for spinal CSF leak, spontaneous leak may also be possible.19–21 Comparatively, pediatric patients have a higher rate of connective tissue disorder than adults with SIH.6 Of the several genetic disorders cited in association with dural ectasia (Table 1), only Ehlers-Danlos type 2, Stickler-like syndrome, Marfan syndrome and Marfan-like syndrome, neurofibromatosis type 1, congenital contractual arachnodactyly-like...
syndrome, and autosomal dominant polycystic kidney disease have been cited in association with SIH.14,22

**Lessons**

Until now, no surviving human with tetrasomy of 10p15.3–10q11.2 has been reported. The only other example involves a fetus with multiple anomalies on ultrasound.9 The unlikely concurrence of a chromosomal anomaly and dural ectasia occurring in the same patient, especially with the diverticula arising at the same anatomical level as the level where the streaky skin pigmentation started, suggests a causal relationship between this mutation and SIH. Cytogenetic evaluation may be indicated in patients monitored for symptoms associated with SIH. Streaky skin pigmentation dysplasia, sometimes termed “hypomelanosis of Ito,” is often a marker for chromosomal mosaicism, which may not be detectable on lymphocyte karyotypes. Thus, a skin fibroblast karyotype may be needed for an accurate diagnosis.

Among the available treatment modalities for SIH, conservative approaches can include bed rest, caffeine, hydration, theophylline, acetazolamide, corticosteroids, and abdominal binder. More invasive measures can consist of epidural injections, intrathecal infusions, and surgical repair.35 In this case, the patient's extensive dural cysts, which spanned close to two-thirds of the spine, and her young age prohibited surgery from being considered a viable option. Alternatively, the severity of her symptoms and extensive dural ectasia deterred us from pursuing any of the more conservative therapies. A fibrin glue patch was considered, but because there was no specific location or diverticula being targeted, but rather an expansive area, a blood patch was deemed more appropriate. We thus elected to pursue a trial of EBP, which provided significant improvement. Mechanistically, limited research exists on this topic. We suspect the patient’s thin, dilated dura, as evidenced by pathologic review, was the result of her genetic disorder, making it more permeable to CSF leakage. In addition, the combination of this and the dural cysts may have affected the hydrostatic pressure, leading to the development of SIH. In this paradigm, the EBP provides at least 3 important functions. (1) It serves as a space-occupying fluid within the spinal canal or “pressure patch,” augmenting the reduced CSF volume through compression of the dura.36,37 (2) The storm of cytokines elements within blood act as an obstructive sealant to fluid volume loss, also known as the “plug theory.”38 (3) The storm of cytokines and inflammation may thicken the dura through sclerosis and/or block the arachnoid granulations, thereby tilting the reabsorption–production balance by reducing the rate of reabsorption.39

Although 30%–90% of patients with SIH can experience initial symptom relief after the first EBP, many often require two or more EBPs to achieve persistent relief.40–42 In pediatric patients specifically, 40% have been cited as being sufficiently treated with EBP alone.4 The immediate symptom resolution experienced by our patient is consistent with a rise of intracranial pressure after the EBP. Conflicting reports exist for the length of time that this effect persists. A series of post-procedural MRI scans by Beards et al.37 revealed that compression resolved after 7 hours. Other reports have cited the presence of extradural space occupying mass up to 4 weeks in an animal model and up to 7 days in a human using myelography.36,43 The recurrence of symptoms at the 1-month mark after both EBPs suggested that the “mass effect” of the clot likely dissipated at this point in time. However, the long-standing improvement in her symptoms may have been the result of a net decrease of CSF leakage through the dural thickening/sclerosis and blockage

### TABLE 1. Known syndromes and genetic mutations associated with dural ectasia

| Authors & Year | Syndrome | Cited with Intracranial Hypotension | Genetic Mutation |
|---------------|----------|------------------------------------|-----------------|
| Schievink & Torres, 199723 | Autosomal dominant polycystic kidney disease | Yes | PKD1 and PKD2 |
| Pyeritz et al., 198824 | Marfan syndrome | Yes (Cheuret et al., 200812) | FBN-1 |
| Avela et al., 201125 | Hajdu-Cheney syndrome | No | NOTCH2 gene |
| Villeirs et al., 199926 | Ehlers-Danlos syndrome | Yes (Schievink et al., 200422) | Several genes (COL5A1, COL5A2, COL1A1, COL5A1, COL5A2) |
| Sheikhzadeh et al., 201127 | Marfan-like syndrome | Yes (Schievink et al., 200422) | Unknown |
| Schievink et al., 20136 | Stickler-like syndrome | Yes | COL2A1 |
| Schievink et al., 20136 | Congenital contractual arachnodactyly-like syndrome | Yes | FBN-2 protein |
| Erkulvrawatr et al., 197928 | Neurofibromatosis type 1 | Yes (Schievink et al., 20136) | NF1 |
| Kono et al., 201329 | Loey’s-Dietz syndrome | No | TGF-β receptor 1, TGF-β receptor 2 |
| Lehman et al., 197730 | Lateral meningocele syndrome/Lehman syndrome | No | NOTCH3 gene |
| Daniels et al., 201631 | Idiopathic bronchiectasis syndrome | No | TGF-β pathway |
| Hajrasouliha et al., 201632 | XXXY syndrome | No | 3 additional X chromosomes |
| Thunström & Axelsson, 201933 | Ataxia-pancytopenia syndrome | No | SAMD9L gene |
| Ravikumar, 202034 | Unnamed | No | CRTP or COL5A2 |
| Present case | Unnamed | Yes | Tetrasomy of 10p15.3–10q11.2 |

Syndromes that have been cited with intracranial hypotension at a date later than when dural ectasia was reported are provided in column 3 from the left.
of the arachnoid granulation pathway. We suspect the return of her symptoms years after her second EBt could be accounted for by an extension of her axial skeleton, with novel dural growth, once again tipping the axis further toward reabsorption due to her dural ectasia. Future molecular changes that occur within the dura after an EBt in relation to changes over time may help better guide treatment in the future and elucidate potential novel therapeutic agents for the treatment of SIH.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Schievink, Nisson, Graham. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Nisson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Schievink. Administrative/technical/material support: Nisson, Graham. Study supervision: Schievink.

Correspondence
Wouter I. Schievink: Cedars-Sinai Medical Center, Los Angeles, CA. wouter.schievink@cshs.org.