Noonan syndrome (NS) is a rare genetic disorder affecting between 1 in 1,000 and 1 in 2,500 individuals worldwide.1 NS may affect more males than females, and it displays a wide array of features depending on the causative gene mutation.2 This disorder is most commonly inherited in an autosomal dominant fashion, although autosomal recessive inheritance and spontaneous mutations are also implicated for certain subpopulations. PTPN11 is the most frequent gene mutation in NS and is found in approximately 50% of affected individuals.1

NS shares phenotypic similarities with other disorders involving Ras/mitogen activated protein kinase gene mutations (RASopathies), including cardiofaciocutaneous, neurofibromatosis type 1, Costello, and Legius syndromes.2 NS is most commonly characterized by short stature, distinctive facial features, intellectual disability, developmental delay, chest deformity, and congenital heart disease, although it can affect nearly all organ systems.2 Multiple case reports have described patients with NS, Chiari 1 malformations (CM-I), and syringomyelia, although the small population size prevents full characterization of this association.3–8

Illustrative Cases
Case 1
A 25-year-old man with NS was found to have CM-I and associated syringomyelia after initial presentation with left leg sensory loss. He underwent posterior fossa decompression with duraplasty and had postoperative improvement in his symptoms. One year after surgery, he reported temperature sensory loss in the left arm, which prompted repeat magnetic resonance imaging (MRI), which demonstrated adequate posterior fossa decompression and C1 laminectomy but persistence of his syrinx with an associated cyst that did not appear fenestrated (Fig. 1). Despite surgical intervention being offered, the family elected for conservative therapy, and his symptoms gradually improved.

ABBREVIATIONS
CM-I = Chiari I malformation; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; NS = Noonan syndrome.

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Five years later, he presented to an outside hospital with acute bilateral shoulder pain, low back pain, diffuse loss of sensation, acute urinary retention, clawing of the hands, and gait ataxia. Repeat MRI revealed an intrasyringeal hemorrhage (Fig. 2). Notably, his syrinx had decreased in size, extending from the cervicomedullary junction to the T2 spinal level. There was also evidence of syrinx dilatation at the rostral end when compared to his postoperative imaging 5 years earlier. The patient received an extensive hematology evaluation that was ultimately unrevealing. His symptoms improved significantly with steroid treatment, and he was subsequently discharged home. At follow-up with us in clinic 1 week later, he demonstrated a stable neurological examination. At that point, the decision was made to pursue repeat MRI with cine sequences once the blood had cleared to maximize visualization and better understand his cerebrospinal fluid (CSF) flow dynamics for preoperative planning.

Six weeks later, cine MRI demonstrated CSF flow obstruction adjacent to the syrinx in the upper cervical spine and expected resolution of blood products. Additionally, the syrinx did demonstrate a caudal cyst that appeared to be noncommunicating with the remainder of the syrinx. The patient still reported pain after a period of conservative management and therefore received repeat posterior fossa decompression with intradural exploration and expansile duraplasty. There was intraoperative evidence of scar tissue within the foramen of Magendie that was fenestrated. A caudal cyst was also appreciated within the upper cervical syrinx, which seemingly did not communicate with the subarachnoid space. The caudal cyst was fenestrated and drained, resulting in a rush of hemosiderin-stained fluid. There were no intraoperative or postoperative complications, and the patient was discharged home on postoperative day 2. Two months after surgery, he continued to demonstrate good relief of his symptoms. His neck and back pain resolved, he no longer experienced urinary retention, his hands were no longer clawed, and he had no issues with gait.

However, 1 month later, his neck and back pain returned, and he began having emesis and temporo-occipital headaches. MRI at that time revealed expansion of the upper portion of the syrinx into the brainstem. In addition, the ventricles were enlarged with periventricular edema. After discussion with family, an endoscopic third ventriculostomy was performed. Prior to that occurrence there had been no clinical concern for elevated intracranial pressure or need for CSF diversion. One month postoperatively, the patient has complete resolution of his neck pain and headaches and continues to demonstrate no other neurological symptoms.
Case 2

A 16-year-old girl with a known history of NS, tethered cord, scoliosis, CM-I, and holocord syringomyelia presented with rapid progression of her scoliosis. She had a history of a tethered cord release 7 years earlier. Lack of syrinx improvement prompted posterior fossa decompression with C1 laminectomy and expansile duroplasty 8 months later. Postoperatively, the syrinx remained stable, and she had no clinical progression of symptoms.

Approximately 5 years after her posterior fossa decompression, her clinical examination remained stable, but she was noted to have rapid scoliosis progression, which was confirmed radiographically. MRI showed unchanged holocord syringomyelia, and CSF flow studies were notable for ventralization and relative decrease of CSF flow at the level of the foramen magnum (Fig. 3). Surgery was recommended but deferred per patient and family preferences. Repeat MRI obtained 1 year later demonstrated no improvement of her syrinx and continued progression of her scoliosis. Notably, T2 MRI sequences were remarkable for intrasyringeal hemorrhage (Fig. 3); she was clinically asymptomatic from this. The patient subsequently received an extensive hematologic evaluation that revealed no specific coagulation disorder but was concerning for multiple low coagulation factors, specifically VIII, IX, IX, and fibrinogen.

Three weeks later, the patient had reoperation in which she received extension of her original posterior fossa decompression via

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs)/ Sex</th>
<th>Presenting Symptom(s)</th>
<th>Other Neurological Issues</th>
<th>Age at 1st Operation (yrs)</th>
<th>Operation Details*</th>
<th>Resolution of Syrinx?</th>
<th>Reoperation?</th>
<th>Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peiris &amp; Ball, 19823</td>
<td>33, M</td>
<td>Neck discomfort, difficulty w/ fine movement</td>
<td>Syringomyelia</td>
<td>33</td>
<td>Cervical laminectomy w/ syrinx decompression</td>
<td>No long-term outcomes included</td>
<td>No long-term outcomes included</td>
<td></td>
</tr>
<tr>
<td>Sakamoto et al., 19974</td>
<td>33, F</td>
<td>Temp/pain sensory loss of extremities</td>
<td>Syringomyelia</td>
<td>33</td>
<td>Occipital craniectomy, C1 &amp; C2 laminectomy†</td>
<td>No long-term outcomes included</td>
<td>No long-term outcomes included</td>
<td></td>
</tr>
<tr>
<td>Holder-Espinasse &amp; Winter, 20035</td>
<td>6, F</td>
<td>Headaches</td>
<td>Syringomyelia</td>
<td>6</td>
<td>Foramen magnum decompression†</td>
<td>N/A</td>
<td>No long-term outcomes included</td>
<td></td>
</tr>
<tr>
<td>Keh et al., 20136</td>
<td>9, F</td>
<td>Found during kyphoscoliosis evaluation</td>
<td>Syringomyelia, kyphoscoliosis</td>
<td>9</td>
<td>Foramen magnum decompression†</td>
<td>N/A</td>
<td>No long-term outcomes included</td>
<td></td>
</tr>
<tr>
<td>Mitsuhara et al., 20147</td>
<td>39, F</td>
<td>Gait disturbance, urinary dysfunction</td>
<td>Syringomyelia, hydrocephalus</td>
<td>32</td>
<td>Foramen magnum decompression &amp; cervical syringosubarachnoid shunt†</td>
<td>No</td>
<td>Yes, hemorrhage into syrinx; emergency T12-L3 laminectomy w/ midline myelotomy &amp; hematoma removal</td>
<td></td>
</tr>
<tr>
<td>Ejarque et al., 20158</td>
<td>29, F</td>
<td>Progressive upper extremity weakness</td>
<td>Syringomyelia</td>
<td>29</td>
<td>Suboccipital decompression†</td>
<td>No long-term outcomes included</td>
<td>No long-term outcomes included</td>
<td></td>
</tr>
<tr>
<td>Ejarque et al., 20158</td>
<td>10, F</td>
<td>Found during evaluation of short stature</td>
<td>None</td>
<td>No operations</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Present case</td>
<td>25, M</td>
<td>Extremity sensory loss</td>
<td>Syringomyelia</td>
<td>19</td>
<td>Posterior fossa craniectomy, C1 laminectomy w/ duraplasty</td>
<td>No</td>
<td>Yes, hemorrhage into syrinx w/ back/shoulder pain, loss of sensation, urinary retention, gait ataxia plus CSF outflow obstruction</td>
<td></td>
</tr>
<tr>
<td>Present case</td>
<td>16, F</td>
<td>Progressive scoliosis</td>
<td>Syringomyelia, tethered cord, scoliosis</td>
<td>11</td>
<td>Suboccipital craniectomy, C1 laminectomy w/ duraplasty</td>
<td>No</td>
<td>Yes, continued CSF outflow obstruction, intrasyringeal hemorrhage, &amp; progression of scoliosis</td>
<td></td>
</tr>
</tbody>
</table>

N/A = not applicable.
* Exactly as provided in article.
† No mention of intradural exploration and/or duroplasty.
C2 laminectomy to ensure adequate caudal decompression with complete lysis of adhesions as well as repeat expansile duraplasty. She received cryoprecipitate and fresh frozen plasma perioperatively. There were no intraoperative or postoperative complications, and the patient was discharged on postoperative day 5. MRI revealed a decrease in the size of her syrinx 5 months after surgery (Fig. 4). She received staged correction of the spinal deformity approximately 1 year after posterior fossa decompression, and she continues to do well clinically.

Discussion

Observations

The association of CM-I and RASopathies has previous limited descriptions in the scientific literature. Despite this, the relationship between NS and CM-I is often underappreciated. There are currently no screening guidelines for asymptomatic patients, and patients with cognitive impairment may have mild symptoms that are unrecognized. Given the known association, however, CM-I patients with cognitive impairment may have mild symptoms that are unrecognized. Given the atypical scar formation and apparent increased risk for reoperation, primary intrasyringeal hemorrhage may result in elevated syrinx formation and apparent increased risk for reoperation, primary intrasyringeal hemorrhage. The reasons for these findings and potential methods to decrease reoperation rates in NS patients remain to be determined.

Lessons

A continuously growing body of evidence supports the relationship between NS and CM-I. Of the reported cases, most of these patients end up presenting clinically with symptoms related to syringomyelia, ultimately prompting surgical decompression. Reoperation rates in these patients appear to be higher than the standard population. Patients with NS, CM-I, and syringomyelia may also have risk for intrasyringeal hemorrhage. The reasons for these findings and potential methods to decrease reoperation rates in NS patients remain to be determined.

References


Disclosures

Dr. Resnick reported other from NIDUS outside the submitted work. No other disclosures were reported.

Author Contributions

Conception and design: Page, Falls, Greeneway, Stadler. Acquisition of data: all authors. Analysis and interpretation of data: Falls, Greeneway. Drafting the article: Page, Falls, Greeneway. Critically revising the article: Page, Falls, Resnick, Stadler. Reviewed submitted version of manuscript: Page, Falls, Resnick, Stadler. Statistical analysis: Page. Administrative/technical/material support: Stadler. Study supervision: Page, Stadler.

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