Two Sides to Every Story: Growing Up with Agenesis of the Corpus Callosum

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Case

Shelly is a 16-year-old female with a long history of developmental disabilities. She presented to the outpatient office with impulsive behavior, intrusiveness, and restlessness that had been increasing over the past 6 months. She would verbalize questions in an intense and pressured manner often with increasing loudness in her voice. She also had seemingly spontaneous episodes of yelling and, in the midst of a verbal outburst, would be very difficult to redirect.

She would perseverate, asking questions repeatedly, sometimes in bursts of several questions in a row, over and over requesting the same answer. Examples of questions included, "Am I ok? When are we going home? Where are we going?" She would ask questions and require prompt answers, presumably to receive reassurance, nearly constantly, for hours a day. Caregivers around her would become exhausted with her apparently insatiable perseveration on the same questions over and over, gradually getting more frantic in her verbalization.

Shelly has congenital neurodevelopmental disorder that includes presumed sequelae from partial trisomy 16. In Shelly's case, the trisomy P-16 was a de novo mutation resulting in additional genetic material on the short arm of chromosome 16. Her parents did not have genetic anomalies or any family history of neuropsychiatric illness. She was born in breech position, but at full term and without perinatal complications, although her mother remarked that she did not "turn" while in utero. Early in infancy, she had physical delays including not rolling over until age

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8 months. She was noted to have low muscle tone and neurologic evaluation was done. She received genetic testing as well as a brain MRI which was notable for marked agenesis of the corpus callosum. A subsequent MRI at age 10 confirmed colpocephaly and agenesis of all but a 1.2 cm segment in the midline of the corpus callosum which appeared to be intact. The corpus callosum is typically approximately 10 cm long, meaning that Shelly's represents a near-total agenesis. No other CNS lesions were identified.

Significant gross and fine motor delays persisted. She did not walk until age 2, after which gradually gained reasonable ambulatory stability, and ultimately became right-hand dominant. She began speaking at 1 year, although articulation was problematic. She needed assistance with some activities of daily living, including dressing and toileting, though these improved over the next few years with speech and occupational therapy.

Neuropsychological and developmental evaluations noted consistent delays in cognitive function. At age 5, Vineland Adaptive Scales and Bayley Scales of development showed functionality in the 2–3-year-old age range with some word skills as high as the 4-year-old range. As a preschooler, she was socially very interested though could not always figure out how to play with others. She engaged in parallel play and often watched others, trying to imitate them. By age 7, full scale IQ was reported in the 55–65 range with verbal abilities consistently better than nonverbal abilities.

At age 5 she was noted to have staring spells. An EEG noted right temporal-parietal and left central epileptiform discharges. The spells stabilized with carbamazepine; however, subsequent EEGs continued to show sharp waves bilaterally in anterior regions. Of note, for many years including the present day, she has episodes where she will suddenly look up or have twitches in her face or neck, accompanied by very brief staring.

From ages 5 to 8, epilepsy stabilized, but her behavior and severe anxiety became more problematic. Shelly had always been anxious regarding medical or dental visits, getting haircuts, and in transition times. When anxious, she would raise her voice, cry, repeatedly say "I want to go home," and be difficult to calm down. At this time, Shelly's parents reported that she had a short attention span, requiring repeated directions to accomplish even simple tasks.

In addition to behavioral treatments and individualized educational programming, medication treatment in addition to anticonvulsants was begun. At age 6, a treatment trial of guanfacine was attempted with limited success. Shelly continued to have significant difficulty with hyperactivity and inattention. Her anxiety persisted to such a degree that sertraline was briefly given but discontinued because of vomiting. Because of perseverative and disruptive behavior that severely impacted Shelly's functioning, risperidone was started at age 9. There was some improvement in sleep onset but only slight improvement in anxiety.

Clinical Pearl #1
A challenging aspect of pediatric neuropsychiatry is the dearth of research on the type of patients represented within the clinical population. As a result the typical psychiatric or neurological algorithmic treatment approach is usually fraught with logical confounds. For example, the fact that Shelly responded well to fluoxetine, but not to escitalopram, reflects a common finding in practice. This was a case where the less neurotransmitter-specific or "dirtier" pharmacotherapeutic agent was more effective. Clinical trials do not exist to prove that point; however, given the heterogeneity of child neuropsychiatry cases, often one must wed theoretical approaches with trial and error for optimal outcomes.

At age 11, she was tapered off risperidone as it seemed to have waned in efficacy. Shelly's days were still characterized by emotional "roller coasters." Escitalopram was also attempted presumably to target anxiety but was discontinued after 6 months because of lack of efficacy.

Since age 12, Shelly's physical health and seizure control improved, though she continued to have behavior difficulties, usually related to inattention and anxiety symptoms that led to perseveration about impending events. She did not have compulsive routines, rigidity, or other compulsive behaviors. She demonstrated no dysphoria or hypomania. Sleep, appetite, and energy were intact. She did not have fears or phobias beyond her verbalizations and need for reassurance via responses to her questions. Medication trials subsequently included buspirone and aripiprazole but yielded only moderate improvement.

Behavioral interventions such as precise daily routines and predictable scheduling were quite helpful. Her verbal skills continued to improve, though she was very concrete in her interpretations. For significant periods of time, she thrived in a specialized curriculum emphasizing life skills and directed work activities.

Shelly's acute social sense and intense interest in the feelings of others became gradually more apparent during Shelly's adolescence. Some of her perseverative statements would include repetitively questioning others about their happiness or contentment, with the hope that they were happy and feeling good. She consistently enjoyed watching people and going into public spaces. However, despite her social interest, Shelly still struggled in school and other social settings because of her verbal perseverations and repeated, nearly echolalic phrases. At times she became so agitated and loudly assertive with her verbal queries that she was very difficult to redirect. She continued to exhaust caregivers and peers by her persistent questioning that often superseded personal boundaries and logic.

Because of the extent to which anxiety was considered to be the common thread driving many of the maladaptive behaviors, another course of guanfacine was started. The treatment goal was that the alpha-2 agonist could target impulsivity as well as anxiety and prevent some of the physiologic discomforts associated with her anxiety response. This time, Shelly had reasonable improvement with guanfacine; however, again, the improvement plateaued after about 6 months. She gradually became more frenetic with verbal perseveration to the extent of repeating herself over 100 times in a day, sometimes 100 times an hour. At that point, it was observed that the perseveration and anxiety were disrupting her sustained attention. With this in mind, distractibility was then targeted by a stimulant medicine, dexmethylphenidate.

After about 10 days of treatment, her distractibility improved. She had more prolonged and goal-directed flow of thought though still had pressured speech at times. She continued taking 10 mg of dexmethylphenidate extended release as well as 2.5 mg of immediate release in the afternoon. At that point, the guanfacine was discontinued. She gradually improved in terms of successful social interaction. She made some peer connections and established reasonable relationships with adults in her school setting. She was observed to have more sustained attention in social settings which appeared to mitigate anxiety.

Shelly continued to improve over the next 6 months, though she occasionally had recurrences of frenetic and perseverative statements and a persistence of baseline compulsive behaviors. Her overall gains regarding communication and personal space were to such a degree that the family was able to go on vacations out of town which they would have previously found impossible. After each vacation, in some cases overseas, Shelly seemed to markedly improve in terms of functionality and emotional stability. She appeared to be enthralled by new settings and, ultimately, reached a new level of calm after returning home.

While she had been improving with affective stability and profited from the exercise of "practicing conversations," it did seem that the behavior patterns bordered upon compulsion. At that point, fluoxetine was begun and maintained at 5 mg daily without side effects. The obsessionality improved though she continued speaking somewhat rapidly and at times repeating herself. However, the content was not driven by anxiety but instead reflected intense interest in conversational topics.

At present, Shelly still takes anticonvulsants, but 8 months ago, she discontinued fluoxetine and all other medicines. She has recurring bouts of perseveration and intense questioning, sometimes escalating rapidly and impulsively, but has continued to function reasonably well in most settings. Shelly continues to sustain gains in social relatedness and verbal interaction. She is still very interactive and enjoys social environments. She continues to have anxiety in less structured settings, and these are more routinely characterized by an increase in requests for reassurance. However, since her discontinuation of psychotropic medications, her symptoms have gradually increased over the past several months, with resultant decrease in functionality. At this point, additional treatments or revisiting previous medication treatments are again being considered.

Clinical Pearl #2

Shelly's response to medication was typical of the pattern experienced by many patients. She had gradual improvement in target symptoms over 1–2 weeks, sustained gains for about 6 months, and then gradual return of symptoms. At that point, medications were usually deemed ineffective and discontinued. They were not usually attempted again until approximately 3–4 months elapsed.

It could be considered that a tolerance phenomenon may be occurring with psychotropic medications. However, this is very likely an oversimplification. If tolerance were occurring, then increased dosages would have yielded renewed efficacy. Yet for Shelly, dosage increases did not have increasing efficacy. The fact that medication discontinuation did not result in symptom exacerbation suggests a more complex mechanism as well.

In many pediatric cases, growth and development means that the treatment targets significantly change. New medicines are sometimes necessary to address new neural targets that may not have existed earlier in development. Alternatively, cycling through trials of the same, or related, medicines, as was done with guanfacine and stimulants, may be more effective. Limited caliber evidence exists to guide treatment in pediatric neuropsychiatry, yet an approach to cycling medicine may nonetheless be a novel approach that is warranted in special cases. It may be inaccurate to consider that once a medicine is deemed ineffective, it will never be effective again.

Trisomy p16

Typically, trisomy of chromosome 16 is incompatible with life, but mosaicism or partial trisomy may occur, albeit rarely. The associated medical conditions are quite varied, including pulmonary valve stenosis and renal dysfunction. Because it is generally fatal in utero, very few publications exist on neuropsychiatric effects associated with partial trisomy 16, though like many other genetic disorders, developmental disabilities may be common [1].

Agenesis of the Corpus Callosum

Agenesis of the corpus callosum is uncommon, present in perhaps 1/4000 of the general population. However, in the context of developmental disability, at least partial agenesis may be present in 2–3/100 [2]. The corpus callosum grows from anterior to posterior, so if partial agenesis is present, usually the posterior segment

is absent. The corpus callosum itself contains upward of 200 million axons and is the most important connection between the two cerebral hemispheres. Although in many animals, several million axons cross the midline in white matter bundles, the corpus callosum is considered unique to placental mammals [3].

The corpus callosum has been implicated in several psychiatric illnesses. Differences in the thickness of the corpus callosum have been noted in pediatric bipolar disorder [4] and in Tourette syndrome [5]. Impulsivity and compulsion have also been frequently reported.

Agenesis of the corpus callosum has been associated with a number of genetic syndromes but is ultimately nonspecific [6]. Deficits in social interaction skills as well as altered language processing have been noted, suggesting a diagnostic overlap with autism spectrum disorders [7]. However, many with agenesis of the corpus callosum seem to be quite functional socially, distinctly unlike typical individuals with autism spectrum disorder, suggesting that the clinical significance is likely far more nuanced [8].

Case Reflections

While Shelly is challenged by developmental disability, seizure disorder, as well as likely perceptual or cognitive processing changes related to agenesis of the corpus callosum, much of her disruptive behavior appears to have been anxiety-fueled. She seeks understanding about the world around her with constant questioning, yet her need for reassurance seems nearly impossible to satisfy. She cannot reduce anxiety with self-soothing behavior or with outwardly physical activities. Instead, she wants comfort with words, even though the words seem insufficient. On one hand, she seems to forget that she has been answered, but it may be more accurate to consider that her main difficulty is in fully absorbing and perceiving the verbal information. She seeks reassuring words, but the words do not appear to translate to emotional comfort, and the nonverbal cues also do not seem to be well-perceived.

What is clear is that for Shelly, social sensibility and mitigation of social anxiety depend upon more than just verbal information. Shelly's challenge is not necessarily in perceiving information or even in reading social cues, but it is in correlating the social cues and verbal information. This can be hypothesized to be related to a deficit in integrating information between left- and right-brain-mediated information. Although Shelly's difficulties are heavily anxiety-related, the mismatch between processing capability and interaction between verbal and nonverbal information tend to further perpetuate her anxiety. Her response is then to repeatedly, verbally request reassurance and comfort, though unfortunately, the reassuring words in reply are only briefly effective in reducing her anxiety.

Although some may consider Shelly's psychiatric illness to be generalized anxiety disorder or even obsessive compulsive disorder, she has far too many neurologic and developmental conditions that confound traditional categorical psychiatric diagnoses. Anything beyond an unspecified anxiety diagnosis and attention deficit hyperactivity disorder could not be well established. She has not had additional

OCD symptoms that would affirm this diagnosis, and the time course of symptom exacerbation and remission would have been atypical.

Social sensibility is ultimately a bi-hemispheric phenomenon. Although Shelly has multiple disabilities, including trisomy 16, epilepsy, and motor delays, her functional challenge is most prominently in social interaction. Ironically, that is also her great strength. Perhaps, because she has intrinsic social skills that are advanced as compared to her other abilities, she remains more reliant upon them to interact with the world. Perseveration may have been a logical consequence to her deficits in processing socially-mediated information and observations. The fact that she struggles to apply abstraction to verbal information leads to significant further anxiety. Occasionally she responds to tone of voice with improvement in perseveration; however, that often does not last much longer than the brief period of calm offered by the semantic content of verbal responses to questions.

One social interaction is particularly representative of the unique perceptual challenges faced by Shelly. During a period of relative stability, Shelly and her family were traveling out of state. As was frequently the case, they would engender positive reactions from strangers in response to Shelly's gregarious engagement. Shelly's social skill and pleasant demeanor often shine in such circumstances. She struck up a conversation with a stranger who was nearby and was asked where she was from. Shelly replied, "I'm from Pennsylvania, where are you from? When the other person replied that she was from New York, Shelly was perplexed. She continued to repeat the question over and over again, getting slightly agitated as the person continued to state that she was from New York. Ultimately, Shelly's parents intervened and mitigated the awkward exchange, but the innocent misunderstanding was illustrative.

Shelly understood that she, herself, was traveling from her home and that place was called Pennsylvania. To her, though, the concept of "home" was linked to the word "Pennsylvania." As a result, she expected the stranger, coming from her respective home, to state that she was also from Pennsylvania and the report that she was from New York was conceptually dissonant. She struggled in connecting the abstract concepts with the concrete locations and, so, when unable to rectify these, became perseverative and agitated.

Lessons Learned About Neuropsychiatry

Integration between the two hemispheres appears to be crucial for the complex process of social and emotional functioning. In many cases, we use words either to express or "think through" anxiety-provoking situations. We also incorporate the words spoken to us by others to mitigate and more broadly understand our feelings of anxiety. But we also use those words in context and perceive additional nonverbal feedback to verify that we are safe, to become calm, and to be confidently reassured.

Perhaps the most important lesson that Shelly teaches us is that dramatic improvement is possible. Distinct improvement seemed to occur with antidepressant treatment,

even at low dose. The antidepressant stabilized Shelly in terms of her anxiety and perseveration. However, it seems intuitive that additional connections were made and processing clearly seemed to improve. The antidepressant dose was extremely low, so it is unlikely that the dosage targeted compulsion, as higher SSRI doses are often necessary for obsessive and compulsive symptoms, but instead its utility seemed to be in allowing new and more nuanced thought processing.

It has been theorized that antidepressants work, not necessarily by directly addressing symptoms but by allowing new processing of existing stimuli [9]. In other words, new information is processed in a different light and with a different context. People who have depression or anxiety may respond to any social engagement or new environment with a well-entrenched pattern of melancholy and trepidation, respectively. With antidepressants, the maladaptive patterns of old processing are dispensed, and new ways of processing information can proceed, presumably with a less rigid approach.

Although marked improvement seems related to medication treatment, it is intuitive to consider that enriched experiences also led to significant improvement in Shelly's demeanor and neuropsychiatric symptoms. Her world quite noticeably "grew" when she traveled. She relished the new environments and delighted in the shared experiences with her family. She and her family developed new, often nonverbal, approaches to managing her anxiety. Enriched environments and novel experiences, as can be had with travel, are known to be associated with significant neurogenesis [10].

Observations from Shelly's Family

Shelly's family notes that she still has a repertoire of questions that she asks every morning, and there are good days and bad days. Sometimes Shelly's mother sends a note to school, warning that it may be a bad day, but then often it does not develop as such.

In reviewing details of this chapter, Shelly's mother noted that she was surprised about the emotional reaction she had when reading the report. More than anything, she remembers being isolated from others and feeling alone in managing Shelly's challenging behaviors. She also recalls her own exhaustion as well as that of her husband and of Shelly's typically developing sibling. Overall, she hopes that families in similar situations can find a supportive community, as the isolation was one of the hardest challenges that she and her family faced.

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