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Agenesis of the corpus callosum is associated with developmental delay and intellectual disability

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ABSTRACT

Keywords: Agenesis of the corpus callosum, development delay, neurodevelopment, intellectual disability

Clinical Context
Liam Johnson (pseudonym), a five-month-old Caucasian infant boy born at 36 weeks gestation with complete agenesis of the corpus callosum (ACC) presented to the Emergency Department with new onset seizures that had been occurring over the previous two days. The diagnosis of ACC was made prenatally by head ultrasound and confirmed postnatally by MRI, which also revealed other cerebral anomalies, including ventriculomegaly and diffuse loss of supratentorial white matter. Subsequent genetic testing revealed a microdeletion of chromosome 14q12-13.3, which was not associated with a known genetic syndrome. Liam was meeting developmental milestones per the parents’ report and was otherwise healthy in the interim until he began experiencing staring spells accompanied by right arm jerking, both lasting for about one minute. He was admitted to the neonatal ICU and neurology was consulted to perform a work-up for seizures. Once the patient was responsive, further examination suggested that he was delayed in several milestones, including visual tracking of objects and head holding without support. Afterwards, the parents became concerned about their child’s development and wanted to know whether they could expect their child to have intellectual disability. Our team therefore sought to answer the degree to which isolated agenesis of the corpus callosum affects developmental prognosis.

Clinical Question
To what degree does complete agenesis of the corpus callosum cause intellectual disability and developmental delay?

Research Article

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Related Literature

PubMed was searched using the terms ("agenesis of the corpus callosum" AND ("developmental delay" OR "intellectual disability")), which yielded 261 results. Case reports, animal studies, articles focusing either solely on ACC as a manifestation of genetic syndromes or on dysgenesis of the corpus callosum and articles whose primary measures did not include assessment of developmental outcomes or were too narrowly focused to address the clinical question were omitted from consideration. Additionally, although meta-analyses were used to guide the literature search and enhance understanding of the topic, they were excluded from consideration for appraisal to allow for a more focused review. After assessing the search results by title and abstract, 258 articles were excluded based on title and abstract not being relevant to the clinical question or the article not being a primary study and 3 studies were selected for further consideration.

A case series from the United Kingdom by Taylor and David surveyed 56 patients with ACC. Patients were identified using the British Neurological Surveillance Unit (BNSU) and intellectual disability was assessed using Intelligence Quotient (IQ) testing. The study found that half of adult patients with ACC had an intellectual disability, two thirds had epilepsy, and one third had a psychiatric disorder. This study was limited by its relatively small sample size, cross-sectional design, and selection bias, as persons with ACC not identified by the BNSU likely had fewer symptoms.

Another study conducted by des Portes in 2018 prospectively identified 34 patients with ACC prenatally and followed them until school-age to examine rates of intellectual disability. The study found that two third of patients enrolled had normal IQ. However, the study had a limited sample size and focused specifically on isolated cases of ACC that did not have other cerebral abnormalities, while our patient had additional abnormalities.

It was determined that a 2016 article by Romaniello et al. was most suitable to answer the clinical question and was chosen for appraisal. This study was a continuation of a 2006 study by Bedeschi et al. that identified 63 patients with ACC and documented genetic profiles and clinical outcomes. The Romaniello study increased enrollment to 162 patients with agenesis of the corpus callosum and divided them by whether ACC was complete or partial and by whether the patients had additional cerebral and extra-cerebral malformations. Outcomes measured included whether developmental milestones were delayed, language abilities, cognitive abilities and neuromotor abilities. The study was selected particularly for its larger sample size and because it divided patients into more specific subgroups based on clinical phenotype allowing us to be able to answer questions about our patient more accurately.

Critical Appraisal

The article by Romaniello et al. used a large case series with long term follow up in which 162 patients with either complete or partial ACC, most identified in infancy, were followed for a mean of 12 years, with a range of one month to 20 years. Because every patient was recruited from a neurorehabilitation center in which patients had already been confirmed to have neurological disorders, there is a significant recruiting bias inherent in the study design, as it is likely that this pool of patients would have a higher rate of developmental impairment than the general population of patients with ACC. Radiologists blinded to the patients’ identities and clinical features reviewed each patient’s imaging to confirm the presence of either partial or complete ACC and to exclude patients with a dysmorphic corpus callosum. Because a medical intervention was not relevant to the question at hand, a case series instead of a randomized controlled trial was appropriate to assess the rate of neurodevelopmental disability in this population of patients. Based on this study design, this article has a Level 3 designation according to the criteria set by the Oxford Centre for Evidence-based Medicine. Additionally, it provided the largest sample size observed in a non-meta-analysis that was identified in the literature search, giving the study relatively good generalizability.

Fifty-six percent of the patients were male, and the age at last follow-up ranged from four months to 42 years. The subjects were stratified into complete ACC versus partial ACC and were then further classified by the presence (termed “plus” patients) or absence (termed “isolated” patients) of additional cerebral malformations and the presence or absence of extra-cerebral malformations, termed syndromic and non-syndromic, respectively. Using this characterization scheme, our patient was considered to have non-syndromic, complete-plus ACC. Eighty-four (52%) of the total 162 patients were classified as complete, and 34 of these were characterized as plus. Nine of these 34 patients were then labeled syndromic, corresponding to our patient’s specific characterization. With this classification system, results could be more accurately applied to ACC patients’ specific neuroanatomical

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and genetic characteristics. However, since only nine subjects shared the same characteristics as our patient, and since no patients had the exact malformations as our patient (ventriculomegaly and diffuse loss of supratentorial white matter), the external validity of the study is somewhat limited.

Developmental outcomes were reported for eight subgroups based on phenotype. These data were reported as the percentage of each group that met either normal development or mild, moderate or severe delay for motor, cognitive, language, and affect milestones, according to the Griffith Mental Development Scale. In the group corresponding to our patient’s characteristics (non-syndromic, complete-plus), severe developmental delay was found in 74%, 74%, 76.5% and 68.5% of complete-plus patients for motor, cognitive, language and affect milestones, respectively and only 10.5% of patients had normal development in each of these domains. Neuromotor deficits were worse in syndromic patients and among non-syndromic patients, plus patients had greater deficits, especially in the partial ACC group. Although non-syndromic subjects also had less cognitive and language deficits than the syndromic group in general, plus non-syndromic patients had a high rate (91%) of cognitive impairment and non-syndromic complete ACC patients had a moderate rate (50%) of language impairment. The authors reasonably concluded that the wide range of etiologies of ACC confers a low specificity to the condition that makes it currently difficult to predict clinical outcomes. Additionally, it is possible such outcomes differ significantly between patients diagnosed with ACC prenatally versus those diagnosed postnatally, but the authors did not group patients into these categories. Furthermore, 41% of the patients in the study had epilepsy but patients were not stratified by epilepsy status. Thus, it is not known whether the presence of epilepsy in this study impacted developmental outcomes.

Clinical Application

Agenesis of the corpus callosum (ACC) is a relatively common brain malformation that has many possible etiologies and is associated with numerous known syndromes and genetic mutations, making it a non-specific condition. The findings reported by Romaniello et al. suggest that developmental delay can be expected to some degree in most cases of ACC. For our patient, it is difficult to anticipate his clinical outcome based on the available research. The Romaniello et al. study suggests that about half of patients with non-syndromic, complete-isolated ACC have normal cognitive development. However, for complete-plus patients, like Liam, outcomes were less favorable, with the majority of patients having severe delays in multiple domains. None of the nine non-syndromic, complete-plus patients in study had the same malformations as our patient, so we it is difficult to say whether or not his prognosis will be similar.

Assuming Liam’s additional malformations make him comparable to the patients in the complete-plus group, the outcome data suggest that for motor, cognitive, language and affect milestones, there is an approximately 70% chance that he would be severely delayed for each domain. We discussed with our patients’ parents the difficulty in completely predicting their son’s development but explained that given his phenotype, he would likely have an intellectual disability. We also informed the parents that this was our best prediction based on current research and that there is a chance he may experience normal development and/or intellect, though it is unlikely. We offered the full range of therapeutic and rehabilitative services to the parents and emphasized that with individualized care we could hope to maximize Liam’s development and quality of life.

Learning points:

1. Developmental delay is likely in patients with agenesis of the corpus callosum (ACC) regardless of etiology.
2. Partial ACC, ACC associated with a genetic syndrome, and ACC accompanied by additional cerebral malformations have a worse developmental prognosis.
3. Future studies should seek to better delineate different ACC phenotypes to better predict patient outcomes.

References

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