

SHORT REPORT

Agenesis of the corpus callosum: a United Kingdom series of 56 cases

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Abstract

A survey of cases of agenesis of the corpus callosum was carried out to examine its associations, utilising the British Neurological Surveillance Unit (BNSU). Fifty six cases were reported (36 male), 37 were adults. Nearly two thirds had epilepsy; half of the adult cases had intellectual impairment as estimated clinically, and a third a psychiatric disorder. Nine cases (five adults) were apparently normal neurologically, and may have escaped detection but for a coincidental or minor disorder leading to neurological investigation. The BNSU is a valuable aid in the study of rare disorders but in less severe conditions, such methods of ascertainment inevitably underestimate prevalence and are prone to selection bias towards patients with associated morbidity.

(J Neurol Neurosurg Psychiatry 1998;64:131-134)

Keywords: agenesis; corpus callosum

The corpus callosum is the main transverse tract of fibres that connects the two cerebral hemispheres. Callosal efferents that originate in the cerebral cortex connect to the contralateral hemisphere, integrating motor, sensory, and cognitive performances of the brain.¹⁻³ Initial formation of the axons that constitute the corpus callosum starts anteriorly at the genu and continues through posteriorly to what eventually becomes the body, a narrowed isthmus, and a widened splenium. The rostrum develops last, usually folding back under the genu. Once formed, the callosum thickens with increasing myelination, except during a period of axonal elimination near birth. Postnatally the corpus callosum undergoes a burst of growth during the first four years of life. The overall size then is largely established although a reduction in size is seen in subjects beyond the age of 40.⁴

Agenesis of the corpus callosum is a rare congenital anomaly which may be partial or complete.⁵ It is often seen in the context of more pervasive developmental disorders⁶ and is seen with interhemispheric cysts, Dandy-Walker malformations, and midline abnormalities such as cleft palate.^{7,8} It also

forms part of the Aicardi, Andermann,⁹ and Apert¹⁰ syndromes. Causes include genetic abnormalities,^{11,12} particularly trisomies 8, 13, and 18 and there also exist X-linked forms.¹³ Metabolic disturbances,¹⁴ maternal substance misuse,¹⁵ and maternal influenza¹⁶ have also been implicated. The relative proportions of complete to partial agenesis remain unclear, as well as their varying clinical consequences.

Callosal agenesis is often noted after infancy when brain CT or MRI is carried out for a specific clinical indication such as the investigation of epilepsy or cognitive impairment. The precise prevalence of agenesis of the corpus callosum is unknown, with the literature providing widely varying estimates depending on the population studied. One paediatric hospital based radiological survey⁶ found that as many as 21% (23/105) of children scanned had callosal abnormalities whereas postmortem perinatal death studies give incidences ranging from 0.004% to 0.0075%.² Bodensteiner *et al*¹⁷ found an incidence of 1.6% for partial or complete agenesis of the corpus callosum in a review of 445 consecutive MR scans of patients under 17 years old at a university hospital in the United States. They also noted hypoplasia in an equal proportion of scans. A similar adult neuroradiological survey detected frequent "attenuation" of the corpus callosum on MRI but only seven (1.5%) showed dysgenesis.¹⁸

The detection rates of asymptomatic "cases" of agenesis of the corpus callosum are beginning to converge on the true incidence of the disorder with increasing availability and widening indications for non-invasive structural brain imaging techniques such as MRI. A more realistic estimate comes from a survey by Swayze *et al*¹⁹ of over 7000 MRI brain scans carried out in a United States radiology centre for varying non-emergency clinical reasons. Five cases of partial or complete agenesis were detected (0.069%).

The reported clinical correlates of agenesis of the corpus callosum reflect the setting in which they present, but most authorities accept that associated learning difficulty and epilepsy (over 40%^{1,8,11}) are commonly seen. However, more recently, agenesis of the corpus callosum has been linked to various neuropsychiatric disorders, including attention-deficit hyperactivity disorder,²⁰ schizophrenia,²¹ and other severe psychiatric disorders.²²⁻²⁶

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Received 18 March 1997 and in revised form 7 July 1997
Accepted 17 July 1997

The above literature draws heavily on case reports and case series which are highly susceptible to selection bias. Attempting to determine the precise prevalence and clinical associations of abnormalities of the corpus callosum would require a huge population based MRI survey. This is clearly out of the question. However, a potential advance on the existing literature is afforded by the British Neurological Surveillance Unit (BNSU).²⁷ The BNSU uses a system of nationwide active surveillance in the United Kingdom for rare neurological and neuropsychiatric disorders based on clinical contact. Members of the Association of British Neurologists and British Neuropsychiatry Association, and neurophysiologist and paediatric neurologist professional associations are mailed on a monthly basis and asked to indicate whether they have seen any cases of the disorder in question. Positive replies can then be followed up for further information.

We report data gathered using the BNSU in an attempt to consider some simple questions regarding agenesis of the corpus callosum in the United Kingdom. Firstly, what is the relation between epilepsy and learning disability (the two most commonly highlighted associations with agenesis), and what proportion of cases are identified fortuitously and are otherwise asymptomatic? Finally, is agenesis of the corpus callosum regularly associated with any particular psychiatric disorder?

Methods

All cases were ascertained via the BNSU. All senior members of the British neurological, neuropsychiatric, and allied professions (consultants)—about 450 in all—were sent report cards for notification of any case of agenesis of the corpus callosum that they had come across. These addressed report cards were mailed every month for a 12 month period. Monthly response rates were 65%–75%. Once a case was notified to the BNSU by a returned report card, then a standard questionnaire was sent to the notifier requesting simple clinical details. Follow up reminders, with stamped addressed envelopes, were also sent when appropriate; all were returned. Apart from the completed questionnaire, copies of case notes and radiological reports were also sought to help clarify any ambiguities or omissions.

A case was defined as paediatric if the affected patient was less than 17 years old. Paediatric cases were excluded from any analysis of frequency or association of a psychiatric history or intelligence quotient (IQ) within the population, as it was considered that these data would be unreliable. An obstetric complication was defined as definite or equivocal using the standardised Lewis-Murray scale.²⁸ Where possible, verbal and performance IQ were used to categorise any learning difficulty into either mild, moderate, or severe impairment. Otherwise the reporting doctor's clinical judgement was accepted. A history of seizures was simply classified as focal, or generalised, or both, by the reporting physician. Any psychiatric history

was initially established by the reporting doctor, but further clarification was obtained by consultation with the relevant general practitioner and treating psychiatrist if possible. No patients were contacted directly.

Results

There were 37 adult cases and 19 paediatric cases reported. Of the adult cases, 25 were men and 12 were women (mean age 37.7 years); in the paediatric population there were 12 male and eight female cases (mean age 5.5 years).

Out of the 56 cases, 40 (71%) had a radiographically complete agenesis of the corpus callosum, as defined by head CT or MRI. Of the 16 (29%) with partial agenesis, the body of the callosum was most often affected followed by the splenium and then the rostrum.

There were eight cases out of the 56 (14%) with an identifiable developmental syndrome: two Aicardi syndrome, two septo-optic dysplasia, and one case each of Soto's syndrome, Asperger's syndrome, cerebral palsy, and dyslexia. Other associated physical deficits were four cases of congenital hemiplegia, three of developmental delay (in the paediatric patients), three of grey matter heterotopia or migration disorder, two of thalamic dysplasia, and two cases of cleft lip and palate. There was no significant relation between the degree of agenesis (complete or partial) and the presence of any developmental disorder.

In the 37 adult cases of agenesis of the corpus callosum, 19 (51%) had some degree of intellectual impairment, with the remainder being judged to have a normal IQ. Of those with learning difficulties, two thirds had a mild impairment, and one third had a moderate or severe problem. There was no significant relation between any degree of intellectual impairment and any other variable reported in this group of patients, although all six of those with severe intellectual impairment had complete agenesis.

Most cases (32: 57%) had some form of epilepsy: 20 had generalised seizures, 12 had focal epilepsy, and four had focal fits with secondary generalisation. There was no significant relation between the presence of epilepsy and degree of agenesis, gender, IQ, or a history of psychiatric illness. Nine had neither epilepsy nor low IQ; of the five adult cases, two had psychiatric disorders, one 34 year old man was diagnosed through investigation of meningitis, another 34 year old woman had MRI to allay her fear of multiple sclerosis, and the fifth (a 47 year old man) was diagnosed "fortuitously" (reason not given).

Thirty five per cent of all cases had had either a definite or equivocal obstetric complication—that is, there were eight patients who had had a definite obstetric complication and nine who had had an equivocal one. However, data were missing on this issue in eight cases. There was no significant relation between the presence of an obstetric complication and gender, developmental disorder, epilepsy, IQ, or psychiatric disorder. There was

an association between obstetric complications and partial rather than complete agenesis (χ^2 5.6, $p < 0.05$).

Thirty five per cent ($n=13$) of all those adults with agenesis of the corpus callosum had a positive psychiatric history. Of these, three had a psychotic disorder (either schizophrenia or manic-depressive psychosis), five a neurotic illness, such as minor depression or an anxiety state; and four were judged as having an impulsive or emotionally unstable personality disorder. There was also one case of an early onset dementia.

There were no significant associations between a positive psychiatric history and epilepsy, low IQ, gender, or any specific neurological syndrome.

Discussion

METHODOLOGICAL ISSUES

This survey, conducted through the auspices of the BNSU, has considerable limitations as it can only ascertain cases from the neurological and neuropsychiatric clinic population rather than from the general community. Paediatricians, general psychiatrists, and those working in the field of learning disability are not automatically surveyed and therefore many cases, particularly in children, would have been missed. Hence the sample was inevitably incomplete and biased towards certain disorders, which limits the generalisability of the findings. Nevertheless our questions mostly concerned adults with uncomplicated agenesis of the corpus callosum so despite the lack of uniform and complete coverage we are still able to gain useful information. It was found that many of the cases of callosal agenesis reported were discovered by chance during investigation for some related disorder. Twenty were free of epilepsy and 18 were judged to have a normal IQ, although only five had formal IQ testing.

INTELLECTUAL IMPAIRMENT

There seem to be subjects with isolated callosal agenesis whose symptoms are not clearly attributable to agenesis,²⁹ presumably because of compensation using other neural pathways. Chiarello³⁰ reviewing the neuropsychological literature found 29 out of 100 published cases with IQs >70 (although 13 had epilepsy). Three adult cases in our survey had no manifest abnormality consequent on callosal agenesis.

A paediatric survey⁸ based on a personal case series of 45 subjects plus 660 gleaned from the published literature suggested that 15% had IQs >70 . Our survey suggests an even higher proportion, presumably because low IQ would increase the chances of early (childhood) detection. It should be noted that an IQ of >70 is a liberal criterion of normal functioning and few of our cases had a formal psychometric assessment. It is also likely that there are other people with callosal agenesis who will escape medical attention, but who may well have detectable neuropsychological deficits.

CLINICAL ASSOCIATIONS

As expected, a substantial proportion of cases of agenesis (26/56) had epilepsy, in line with previous studies. Looking at this association from the other perspective, Septien *et al*³¹ discovered only 26 cases from a personal series of 2088 epileptic patients who had CT (1.25%). Whether the abnormality was partial or complete does not seem to relate to the presence of epilepsy suggesting that impaired interhemispheric connectivity is not of direct aetiological importance.

There was a 2:1 male to female ratio of adult cases in our survey and a 3:2 ratio in the children, which is in keeping with the usual preponderance of neurodevelopmental anomalies in males.¹¹ However, some authorities have reported no¹ or, in consecutive scanned series, less pronounced gender effects.⁸

There was a high level of psychiatric morbidity in this group. This was, however, not specific to any disorder although psychotic illness was overrepresented. Agenesis in the case of presenile dementia was probably a chance finding although a similar case has been described.³² Finally, the incidence of obstetric complications deserves comment. These were based on medical records so may be of variable accuracy. Nevertheless, macrocephaly, which often accompanies degrees of agenesis,¹¹ makes delivery complications more likely.

In conclusion, a survey utilising the BNSU disclosed 56 cases of agenesis of the corpus callosum. Nearly two thirds had epilepsy. Half of the adult cases had intellectual impairment and a third a psychiatric disorder. There were twice as many male cases as females. Nine cases (five adults) were apparently normal neurologically, and may have escaped detection but for a coincidental psychiatric or minor disorder leading to neurological investigation. The BNSU is a valuable aid in the study of rare disorders but in the case of less severe conditions, there will inevitably be an underestimate in prevalence and a liability to a biased selection of cases with associated morbidity.

We thank Mrs P Mott, Dr Cockerell, and the BNSU for their administrative help. We also thank the clinicians who took the trouble to report their cases.

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