AGENESIS OF THE CORPUS CALLOSUM

IAN A. D. BOUCHIER, M.B., CH.B. (CAPE TOWN)

Senior Resident Medical Officer, Department of Neurology and Psychiatry, Groote Schuur Hospital, Cape Town

Agenesis of the corpus callosum is not particularly common; its incidence in institutions where a great number of air encephalographic studies are done is said to be 3%.[1] It is probable that a number of the cases are not reported.

HISTORICAL

The first case of agenesis of the corpus callosum was reported by Reil in 1812 and was cited by Sheldon and Peyman.[2] In 1933 Baker and Graves[3] reviewing the literature, found 81 cases and reported one of their own in a feeble-minded boy of 17 years who had died of pulmonary tuberculosis. Dandy[4] in 1918 performed the first ventriculogram and was the first person to outline the ventricles with air. Guttman, cited by Davidoff and Dyke[5] found the condition at post-mortem in a patient in whom he had failed to diagnose the condition in life, in spite of having done an air encephalogram. The first ante-mortem diagnosis of the condition was made independently by Davidoff and Dyke[5] and Hyndman and Penfield[6] on the pneumo-encephalographic appearances.

Since then, Bunts and Chaffee[7] and Carpenter and Druckemiller[1] have ably reviewed the literature on the subject, and more recently valuable contributions have come from van Epps,[8] Carpenter,[9] and Hankinson and Amador.[10]

Scattered references to the angiographic appearances of this anomaly are to be found before 1953, at which time Sheldon and Peyman described two cases with their angiographic findings. Carpenter,[9] and Carpenter and Druckemiller[1] reported the angiograms to be normal. Van Epps[8] performed an angiogram on one of his patients and noted the anterior cerebral arteries to be displaced backwards, with no obvious shift from the mid-line, but he laid little stress on this finding. It is to Sheldon and Peyman that we are indebted for the first detailed account of the appearance on angiogram.

CASE REPORT

C.S., a Coloured male of 49 years of age, was admitted to the neurology ward on 6 June 1957. The patient gave a history of being well until 15 to 20 years before admission, when he was involved in a motor car accident, sustaining an injury to the head, with no loss of consciousness. Since that time, he has had attacks (about once every 2 to 3 months) during which he became rigid, fell to the ground with generalized jerking, and while able to hear the voices of people as if in the distance, he was not able to speak. The attacks lasted 20 minutes and were always precipitated by emotional stress.

Six months before admission the attacks became more frequent, occurring up to 3 to 6 times a day, and while there was no essential change in their character, the relationship to emotional stress was lost, and the attacks would occur without any apparent precipitating cause. In addition, however, a marked personality change was observed: he became suspicious, accused his wife (on completely false grounds) of being unfaithful to him, and assaulted his elder children, believing that they were against him. He appeared to withdraw into himself; became so inefficient at his work that he was discharged, and was suspicious of, and quarrelled with all his neighbours.

There was nothing relevant in his past history. The patient neither smoked nor took alcohol. He worked as a bricklayer's assistant. He had 4 children, the eldest being 18 years and the youngest 4 years. Both the wife and the children were in the best of health. There was no family story of mental ill-health, nor were any of his family deformed in any way.

On examination, he was a middle-aged male, in good general condition, with periorbital bruising on the left side, the result of falling during one of his attacks. The patient was correctly orientated as to place, time, and person. While he was able to speak clearly and coherently, he was pathologically suspicious: he showed paranoid delusions, believing that the doctors and nursing staff were against him, and even, on one occasion, the patients. He described voices—both male and female (his sister-in-law)—talking to him, and telling him to beware of the doctors; that his wife was being unfaithful to him; and that he would die soon. He believed that his 'mind was not working properly' and blamed various members of his family for having bewitched him.

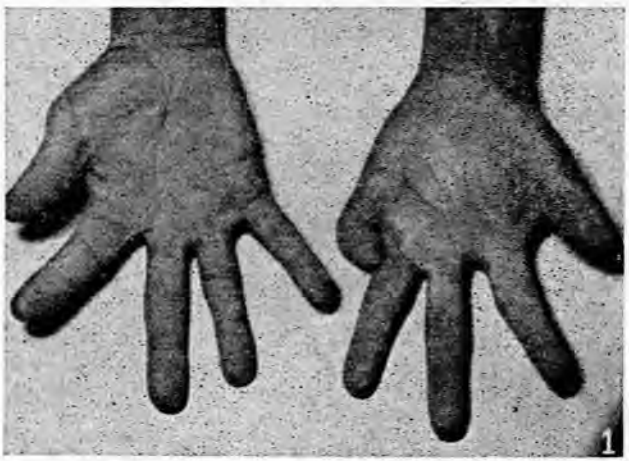

Fig. 1. The hands of the patient, showing the congenital deformities.

There were congenital deformities of both hands: short, webbed thumbs; radial deviation of both forefingers, and the little finger of the left hand was twisted in upon the palm. He was afebrile. Pulse 76 beats per minute. Blood pressure 140/80 mm. Hg. There was no cardiomegaly, and auscultation was normal. The respiratory system, abdomen, and genito-urinary system were all normal. No signs of organic nervous disease were found on routine neurological examination. He was right handed. The urine was normal in all respects. E.S.R. 3 mm. per hour (Westergren). W.B.C. 6,500 cells per c.mm. P.C.V. 51%. Haemoglobin 14·5 g.%. A smear showed the red cells and the platelets

to be normal in all respects, and the differential count was: P. 51%, L. 40%, E. 5%, M. 4%. The blood and cerebrospinal fluid: W.R. negative. Lumbar puncture: pressure 65 mm. of fluid, clear fluid, free flow, globulin 0, protein 10 mg.%, no cells. Blood urea 27 mg.%. Serum albumin 4·5 g.%. Serum globulin 1·9 g.%. Thymol turbidity 1. Zinc turbidity 4. X-ray of the skull normal. X-ray of the chest normal.

X-ray of the hands. The bony architecture was normal. There was asymmetrical development, the left hand being smaller than the right. The left first metacarpal and proximal phalanges were 0·1 inch shorter than the right. The proximal phalanx on the left was 2/3 as long as the right, with broadening of its base and head. The left 5th metacarpal was shorter and more slender than the right. Both proximal phalanges of the indices, the right more than the left, showed defect of tubular moulding. The proximal phalanx of the left little finger was similarly affected, and the middle phalanx showed defect in ossification with non-development of the distal 2/3rds and congenital flexion at the interphalangeal joints.

A pneumo-encephalogram showed no displacement of the ventricular system to either side (Figs. 2 and 3). There was wide separation of the lateral ventricles; there was dorsal angulation and no obvious concavity of the medial wall of the lateral ventricles. Both ventricles showed some enlargement, the left more than the right, and there was dilatation of the posterior horns of both lateral ventricles. The third ventricle was dilated, displaced upwards and showed an indentation on the anterior wall. The interventricular foramen was enlarged. The findings are typical of those of agenesis of the corpus callosum.

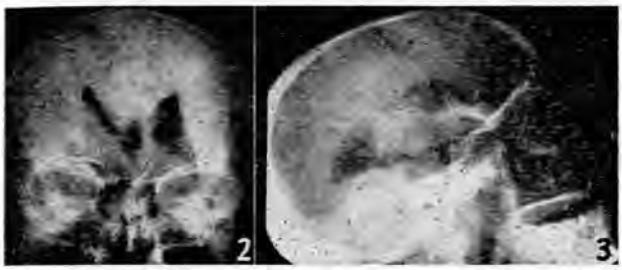

Fig. 2. Air encephalogram (A.P.). This shows the separation of the lateral ventricles, their bicornuate appearance, and the dilated, and elevated III ventricle.
Fig. 3. Air encephalogram (lateral view). Note the dilated posterior horn of the lateral ventricle; and the dilated III ventricle, with the 'anterior excavation'.

On 14 June 1957, under general anaesthesia, bilateral percutaneous carotid angiograms were performed by Mr. de Villiers Hamman (Fig. 4). This showed no displacement to either side of the anterior cerebral arteries. The vessels were well formed on the antero-posterior view, but the lateral view showed both anterior cerebral arteries to have lost their anterior bowing, and they passed obliquely backwards, with the pericallosal arteries making a sharp downwards kink and only 0·9 cm. above the dilated interventricular foramina. The rest of the arterial tree appeared normal.

The electro-encephalogram showed a generally dysrhythmic record with mixed frequencies, and fast activity predominating over central areas. Over-breathing produced posteriorly situated complex waves of higher than average voltage.

Course

During the first week of his stay in hospital the patient had a number of attacks of sudden onset during which the whole body became rigid, with limbs extended and teeth clenched. He lay hyperventilating with his eyes closed. This state lasted from 2 to 4 minutes and could be terminated by loud commands. On one occasion rhythmical jerking of the right wrist was seen. Following the attack the patient would lie still with his eyes closed for about an hour, during which he did not respond to verbal or painful stimulation. The patient settled down well after the first week and his delusions became far less of a burden to him. Paranoid delusions persisted, the patient believing that people thought him to be a spy and at times a ghost. The psychiatric state was treated with hospital care and psychotherapy.

EMBRYOLOGY

Sheldon and Peyman[2] emphasize that an understanding of the embryology of the corpus callosum is of help in explaining the radiological appearances of the agenesis. The late ontogenetic development of the corpus callosum is in conformity with the fact that it is, phylogenetically speaking, the most recently developed of the 3 commissures of the forebrain. It is present exclusively in the higher mammals, and in the lowest group of the callosal mammals (Edentata) it is little more than a membranous structure. The formation of convolutions in the human brain increases the total volume of grey matter threefold, and the size of the corpus callosum is always proportional to this volume.[6]

It is generally agreed that the corpus callosum develops between the 3rd and the 5th month of intra-uterine life.[2,7,8] Anterior to the lamina terminalis a slight thickening of the wall of the hemisphere appears in the mid-line—Hocksetter's commissural plate. The two plates fuse in the mid-line, and this occurs before the closure of the anterior neuropore. The plate is present by the 14th day. This plate is only a conductive tissue to facilitate the crossing of the interhemispheral fibres. These fibres are condensed dorsally as the corpus callosum and ventrally as the anterior commissure, whereas the remnant of the commissural plate between is represented by the septum pellucidum. Thus the corpus callosum, the anterior commissure, the psalterium and the septum pellucidum are all integral parts of the commissural plate, a lesion of which will affect all of these structures. Marburg[11] has stated that cases of genuine agenesis of the corpus callosum are produced within the first 14 days of intra-uterine life.

The anterior part of the corpus callosum develops first, the corpus callosum gradually extending in a cephalic, dorsal, and then caudal direction to form the rostrum and genu; and at the same time part of the nearby cortex on the medial surface of the cerebral vesicles is cut off by the developing corpus callosum to form the two leaves of the septum pellucidum. The body of the corpus callosum continues to grow caudally, carrying with it on its under surface the septum pellucidum and the hippocampal commissure, and the latter eventually lies between the two parts of the body of the fornix.

Development is not complete until the 5th month. Agenesis may be complete—in which case the callosal fibres are heterotropic and appear as a longitudinal bundle; or may be partial, when one or other division is incompletely formed and the rest lacking: sometimes the genu alone is present, sometimes the splenium. The gyrus cinguli in its middle position is either absent or atrophic, resulting in the radial arrangement of the sulci of the medial wall of the hemisphere, as well as the absence of the common section of the parieto-occipital and calcarine fissure. In some cases, hydrocephalus develops.[8]

Some authors have found the staging by Bruce[13] of value in determining the approximate time a lesion would have occurred to cause the existing abnormalities, but not infrequently deviations from his staging occur:

First 3 *weeks:* Complete absence of the corpus callosum with hemispheres and ventricular system in a single unit.

Four weeks to 3 months: Absence of the corpus callosum and anterior commissure, but perfect division of cerebral hemispheres by longitudinal fissure.

During the 4th month: Absence of the corpus callosum, but the presence of anterior commissure.

End of the 4th month: The presence of the anterior commissure and genu of the corpus callosum.

AETIOLOGY[1,8,12]

The reason for the anomaly is obscure. Basically there is an arrest of development due to local impairment of the embryonal metabolism due to reduced oxygenation.[1] But it is the time at which the arrest occurs which is of importance in determining the degree of abnormality. There are numerous explanations for this—all unsatisfactory, i.e. vascular lesions, porencephaly, inflammation, hydrocephalus. Hicks[14] has produced the defect by the irradiation of rats with 100-400 r. on any day from the 9th to the 19th day of gestation; and Naiman and Clarke Frazer[15] in 1955, reporting two cases of complete agenesis in siblings, suggest the possibility of the anomaly being genetic in origin.

CLINICAL FEATURES

There is no significant sexual distribution,[9] and apart from the case quoted above there is no familial incidence. The condition may be completely asymptomatic[2,12] with no impairment of intelligence. If symptoms occur the most frequent are epilepsy—both generalized and focal—and varying degrees of mental impairment.[1,2] In their review, Carpenter and Druckemiller,[1] found that initial symptoms were present in 53% under 2 years of age, in 17% under 10 years, and only in the 2 cases reported did the initial symptoms appear after the age of 20. Bunts and Chaffee[7] agreed that the majority of cases present before the age of 10 years. In a more recent review Hankinson and Amador[10] presented 14 cases ranging from birth to 46 years as the age of onset. They described two groups: (*a*) The infants, who presented either as failing to progress, with irritability and vomiting, or presented with raised intracranial pressure of rapid or slow onset. This constituted the larger group. (*b*) Adults (only 3 cases) who presented as epilepsy of late onset.

Associated anomalies are not infrequent, and these include: (*a*) Associated cranial-nerve defects, incomplete separation of the frontal lobes, hydrocephalus, enlarged anterior commissure, porencephaly, arhinencephaly, microcephaly and dilatation of the cisterna magna.

(*b*) Associated body defects: Cleft palate, hare-lip, cryptorchidism, thoracic stomach and coloboma of the optic nerve.

Rare symptoms include: Spastic paraplegia, hyperreflexia, athetoid movements, nystagmus, strabismus, and the Babinski sign.[7,8,16]

The cerebrospinal fluid is normal in all cases.[9] The electroencephalogram: It is generally agreed that there is no specific pattern and a diffuse dysrhythmia, with irregular slow waves and absence of normal alpha acitvity, is the commonest finding and is probably due to associated brain defects.[7]

Radiographic Features

1. Straight X-rays of the skull are not helpful.[1]
2. Pneumo-encephalography. This is of great value and a certain diagnosis may be made from the air studies. Davidoff and Dyke,[5] who are always quoted in this connection, in 1934 laid down the following diagnostic criteria:
   (1) Marked separation of the lateral ventricles.
   (2) Angular dorsal margins of the lateral ventricles.
   (3) Concave mesial borders of the lateral ventricles.
   (4) Dilatation of the caudal portions of the lateral ventricles.
   (5) Elongation of the interventricular foramina.
   (6) Dorsal extension and dilatation of the 3rd ventricle.
   (7) Radial arrangement of the mesial cerebral sulci around the roof of the 3rd ventricle and their extension through the zone usually occupied by the corpus callosum.

Hyndman and Penfield[6] consider that the bicornuate appearance of the bodies of the lateral ventricles is pathognomonic of the condition. They also describe the appearances of partial agenesis: (*a*) The lateral view of the 3rd ventricle shows an anterior excavation suggesting a small anterior rudiment of the corpus callosum; or (*b*) the posterior part of the 3rd ventricle is wider than normal and curved upward—'fish-tailing', indicating the absence of the splenium, but the presence of a rudimentary or partly formed rostrum or body. Many authorities doubt this, and if the appearance is indicative of partial agenesis then it is more common than suspected.[1,2,9] Enlargement of the cisterna magna may also be shown, and van Epps concludes that it is evidence of associated cerebellar anomalies.[8,10] A generalized hydrocephalus is present in 8·8% of cases.[9]

Angiographic Appearances

Sheldon and Peyman,[2] describing in detail the angiographic appearance in two cases, conclude that the signs are probably diagnostic.

1. The ascending part of the anterior cerebral artery runs almost directly upwards, and then the artery bends sharply backwards, this occurring at a lower level than normal.

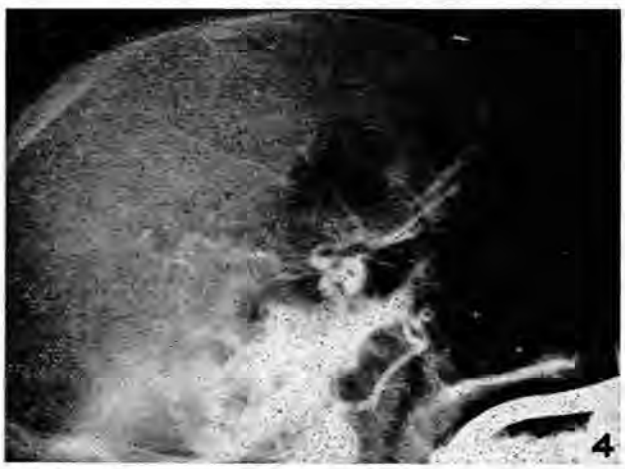

Fig. 4. Carotid angiogram (lateral view). The abnormal course of the anterior cerebral is seen, as well as the close relationship to the dilated interventricular foramen.

2. The curve of the artery round the genu is lost.

3. The remainder of the course of the pericallosal artery lies immediately above the roof of the 3rd ventricle. (Normally the pericallosal artery lies above the corpus callosum and is about 2 cm. superior to the roof of the 3rd ventricle.)

4. Diminution of the normal curve of the great cerebral vein is seen and it is situated in front of and above the usual position.

DIFFERENTIAL DIAGNOSIS

This is easy, as the air studies and angiograms have such a characteristic appearance.

1. *Communicating Cyst of the Septem Pellucidum*

This is the only real problem, i.e. if the 3rd ventricle is confused with the air filled cyst.[7] Here (*a*) the lateral ventricles are not separated and do not have a filling defect in their mesial walls.

(*b*) There is no enlargement of the cyst or ventricles present unless as part of a general hydrocephalus.

2. *Non-communicating Cyst (fluid filled)*[2,7]

(*a*) The 3rd ventricle is not raised.

(*b*) There is no central air shadow between the lateral ventricles.

(*c*) Note the marked separation of the ventricles.

3. *Lipoma of the Corpus Callosum*[23,24,25]

I. Lipoma without agenesis:

(*a*) Shows an area of decreased density in the region of the genu on staigrht X-ray.

(*b*) This is surrounded by a zone of calcification.

(*c*) Pneumo-encephalogram shows dilatation of the lateral ventricles with separation, concave mesial border, but no elevation of the 3rd ventricle though it is enlarged.

(*d*) No displacement of the anterior cerebral arteries as they are often incorporated in a lipoma of the corpus callosum.[26]

II. Lipoma associated with agenesis.

(*a*) The roof of the 3rd ventricle will not be raised as much as usual.

(*b*) It will be flattened by the tumour.

4. *Other Symmetrical Tumours of the Corpus Callosum*

These are rare. There may be some concavity of the bodies of the lateral ventricles in the superior and medial surfaces, but the 3rd ventricle will not be raised in position. As the tumours are infiltrative, the pericallosal artery is seen to be displaced upward and laterally on angiography.

5. *Symmetrical Tumours of the Septum Pellucidum*

There may be some separation of the lateral ventricular bodies, but the most important sign is the lack of filling of the upper part of the 3rd ventricle, and the pericallosal artery is raised and stretched and the anterior part is rounded on angiography.

DISCUSSION

The precise function of the corpus callosum is uncertain. Most authors agree that its fibres connect homologous as well as heterologous areas of both cortices, and it is said to play an important part in facilitating the cooperation of both hemispheres, particularly in man, in whom one-sided cerebral dominance is so prominent.[17] The anterior third is concerned with praxis (i.e. the smooth performance of simple and complicated motor acts) and speech; the middle third with praxis only; and the posterior third with speech and transmission of visual and auditory conceptual impulses to the hemispheres.

In man and monkeys negative results have followed longitudinal section (Cameron and Nicholls, 1921;[18] and Dandy, 1931[19]). However, van Wagenen and Yorke Herren[27] studied 10 epileptic subjects and found that when the anterior part of the body, the genu and the splenium were divided, the seizures ceased to be generalized. Studies on the above patients (with 6 additional ones) were undertaken by Smith and Akelaitis.[28] They found that few if any speech defects occurred, and disturbance of unilateral and bilateral motor skills occurred infrequently, and in such cases were complicated by the presence of pathological conditions not directly dependent upon the callosal section. There was no evidence that common tasks were seriously disturbed. Most patients experienced no mental confusion in connection with the status of their laterality subsequent to the operation (or if there was any post-operative shift it was temporary). Furthermore, no disturbance of absolute or relative orientation, absolute or relative discrimination of size, or recognition of colour objects or letter, was found in either homonymous field of vision.[29] But Meyers[30] working with cats found that, after section of the corpus callosum, there was a failure to transfer simple visual problems. It has also been shown that dyspraxia in the 'subordinate or dominant hand after partial or complete section of the corpus callosum occurs only when damage to the subordinate or dominant hemisphere occurs'.[31] The conclusion of these workers is that bilateral integration of such activities as motor performance occurs through commissural systems at levels below the corpus callosum.[30,31] One must therefore assume that the corpus callosum is not the only pathway for inter-hemispheral connections.

The clinical picture varies in patients with agenesis of the corpus callosum and in those in whom pathology of the corpus callosum is acquired. In the latter group the following symptoms are described: Mental disturbance, motor paralysis, drowsiness, motor apraxia, occasionally cerebellar dysnergia, and often paralysis of the cranial nerves and moderate papilloedema—all with sufficient frequency to be considered a distinct syndrome by some.[20,21] Remitting mental symptoms are one of the striking features of Marchiafava's disease (primary degeneration of the corpus callosum), but the degeneration in the centrum ovale, as well as vascular and nutritional deficiencies, complicates the clinical picture. Similarly the symptoms resulting from destruction of the corpus callosum fibres by inflammation and tumour growth are due to the presence of signs referable to disease of neighbouring parts of the brain. Carpenter, from his studies of patients with agenesis, could find no support for the view that there is a specific disease syndrome associated with callosal pathology. He states that the relationship between the corpus callosum and mental symptoms is difficult to determine, but that in some obscure way mental disturbances and intellectual deterioration are associated with most of the pathology in states

involving the corpus callosum, including agenesis.[9] In this connection a recent paper by Russel and Reitan[22] is of interest. They state 'There is obvious disagreement between conclusions regarding the functions of the corpus callosum when one compares the studies made on persons with callosal tumours, and callosal surgical section. The preponderance of mental symptoms (including mental dulling, apraxia etc.) noted with callosal tumours is not reported with callosal section. Since tumours are so likely to involve other structures as well as the corpus callosum, one must respect the results from the surgical sections. Nevertheless, in these studies, as with others on the psychological significance of the corpus callosum, standardized psychological tests of demonstrable validity in measuring the effects of organic cerebral damage have not been used'.

Their paper is the first study of congenital agenesis (in a 19-year-old female) using standardized tests as suggested above, and while they agree that to generalize from one case is unjustified, they suggest that the following are changes which may possibly be associated with agenesis:

1. Severe impairment of biological intelligence, particularly of the abstraction pattern, but with sparing of the power factor.
2. An I.Q. in the moronic range.
3. Deficiency in bilateral transfer.
4. Impaired visuo-motor coordination.
5. Impaired ability to sustain concentrated attention to a task for 10-second intervals.
6. Depression, anxiety and emotional instability.

However, the widely accepted view at present is that agenesis of the corpus callosum *per se* is symptomless, and such symptoms as are present may be ascribed to associated developmental defects of the brain.

The case reported is of interest in that the anomaly is present in a person suffering from an obvious paranoid schizophrenic state, and no connection between the two conditions is postulated. In addition, no previous reference to congenital anomalies of the hands in association with the cerebral defect has been encountered in the literature. It is difficult to understand what the exact nature of his attacks following the accident were, and it is hard to believe that there was any relationship to his schizophrenic condition, which was of relatively recent onset. The conclusion is that he experienced episodic disturbances of consciousness which were probably epileptic and consequent on the head trauma. The other possibility remains that he was one of those unusual cases of agenesis where the epilepsy is of relatively late onset.

The pneumo-encephalographic findings are typical of the condition, except for the absence of concavity of the medial borders of the lateral ventricles, but a possible reason for this is that the view was taken too posteriorly for the bodies of the lateral ventricles to show up clearly. While the typical 'fish-tail' appearance is not seen in this case, the excavation of the anterior wall of the 3rd ventricle on the lateral view appears to be definite enough to warrant the diagnosis of a partial agenesis of the corpus callosum being made on this patient. The angiographic appearances are easy to understand, as in the absence of the corpus callosum the artery must lie in close relationship to the roof of the 3rd ventricle, while the anterior curvature which is formed by the rostrum will be lost. This patient shows these features very well.

SUMMARY

1. A case of agenesis of the corpus callosum is presented and the reasons for considering the anomaly to be a partial and not a complete agenesis are discussed.
2. The condition in this case was associated with congenital anomalies of the hands and the presence of schizophrenia.
3. The pneumo-encephalographic and angiographic appearances are described.
4. The functional significance of the corpus callosum is discussed.
5. The differential diagnosis of this anomaly is considered.

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