Agenesis of the Corpus Callosum in Two Sisters

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Summary. Two sisters are described. They are offspring of Arabic parents who are both first and second cousins, through both sets of grandparents; additionally the father's parents are first cousins. The diagnosis of agenesis of the corpus callosum in the propositae was made by the characteristic picture on the pneumoencephalogram.

The clinical symptoms in the two sisters varied considerably. The older sister had shown delayed psychomotor development in infancy, mild mental retardation, and developed seizures at 7 years of age of both the grand mal and akinetic types. Her physical and neurological examination did not show any abnormalities. The EEG was severely abnormal with slow wave activity over the posterior parts of the brain and focal spiking. The younger sister presented at 6 months of age with failure to thrive, generalized hypotonia, but without seizures. Her EEG was within normal limits.

This anomaly was probably transmitted by an autosomal recessive gene. The clinical and genetic aspects of this syndrome are discussed.

Sporadic cases with the anomaly of agenesis of the corpus callosum (ACC) are not uncommon, and 210 such cases had been reported by 1965 (Harcourt-Webster and Rack, 1965). However, the familial form of ACC is very rare. Only five such families have been reported until now (Zellweger, 1952; Naiman and Fraser, 1955; Ziegler, 1958; Menkes, Philippart, and Clark, 1964; Dogan, Dogan, and Lovrencic, 1967). We wish to describe another family in which two sisters, offspring of a consanguineous marriage, had ACC manifesting itself as two distinctly different clinical syndromes. While one sister had mild mental retardation and seizures starting at 7 years, the other sister presented with failure to thrive and motor retardation at 6 months.

Case Reports

The sisters belong to an Arabic family originating in a village near Jerusalem. The parents are complexly related (see Fig. 1) and the coefficient of inbreeding F of their offspring is $\frac{3}{32}$. The mother had nine pregnancies including one miscarriage. Two females (IV.1 and

IV.4) died in early infancy, two males (IV.2 and IV.7) and two females (IV.3 and IV.6) are alive and well, and the other two females (IV.5 and IV.8) are the propositae.

Case 1 (IV.5), was born in 1960, after an uneventful full-term pregnancy and normal delivery. Birth weight was 3.8 kg. The postnatal course was normal. Psychomotor development was delayed. She sat at 9 months, stood at 18 months, and walked and spoke at 30 months. She has always been moderately retarded and had nocturnal enuresis. At 7 years of age, she began to show recurrent seizures of the akinetic and grand mal types which were only partially controlled by anti-convulsant medication.

On physical examination, she was normally developed for her age. She had a broad base gait, bilateral

FIG. 1. Pedigree of the family. The dates of birth of the fourth generation are indicated on the pedigree.

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horizontal and upward nystagmus, symmetrical decreased deep tendon reflexes, and right upgoing toe. Both optic discs were pale. Laboratory tests including fasting glucose, urea, proteins, magnesium, phosphorus electrolytes, calcium and blood cell counts were unremarkable. Blood and urinary chromatograms for amino acids and urine for reducing substances were all normal. The cerebrospinal fluid was normal except that the amino-acid content of arginine, lysine, and glutamic acid were elevated.

The electroencephalogram was severely abnormal with slow 4–6 Hz wave background activity in the posterior parts of the brain and a spike focus in the left temporo-occipital region.

The electroretinogram was normal in both eyes. The visual evoked potential (VEP) when stimulating the right eye was lower at the left occipital cortex. When the left eye was stimulated, the VEP obtained from the right occipital cortex was low.

The pneumoencephalogram showed wide separation of the lateral ventricles on the AP view. The superior portions of the ventricles have a pointed appearance rather than a normal flat roof (Fig. 2). The third ventricle is dilated and lies between the lateral ventricles rather than beneath them. There is increased sub-arachnoid air-collection at the right parietal area suggesting a leptomeningeal cyst.

Bilateral carotid arteriogram showed that the anterior and middle cerebral arteries were stretched and the pericallosal artery displaced posteriorly.

Despite anticonvulsive treatment, the girl had recurrent seizures with progressive mental deterioration.

Case 2 (IV.8), was born in 1966, after a normal delivery. The pregnancy was uneventful except for ankle oedema and proteinuria in the third trimester. Birth

weight was 3.8 kg. The postnatal course was unremarkable but later she showed poor appetite, constipation, and slow weight gain. At 8 months of age, she was not able to roll over, sit, or control her head.

On physical examination at 8 months, weight was 4.5 kg, height 62 cm, and head circumference 38 cm; all far below the third centile. The shape of the head and face were unremarkable. The anterior fontanelle was open 5 mm. She had generalized hypotonia with normal deep tendon reflexes. Both optic fundi were normal and she followed objects well with both her eyes. Routine blood counts and chemistries were unremarkable. The acid base balance, intestinal, renal, and endocrine functions were all within normal limits. The cerebrospinal fluid was normal. Urinary chromatograms for amino acids and sugar were all normal. The electroencephalogram was normal. The pneumoencephalogram (PEG) showed the characteristic features of ACC (Fig. 3).

FIG. 2. Case 1. Posterior-anterior view of the pneumoencephalogram demonstrating typical appearance of agenesis of corpus callosum with third ventricle lying between lateral ventricles and superior portions of lateral ventricles spread apart.

FIG. 3. Case 2. PA view of the pneumoencephalogram.

Discussion

The development of pneumoencephalography facilitated the diagnosis of ACC during life. Both sibs presented, fulfil the pneumographic criteria of callosal agenesis as established by Davidoff and Dyke (1934). The carotid arteriogram which was performed in case 1 was characteristic of this syndrome as outlined by Sheldon and Peyman (1953).

Out of 210 cases with ACC that were reported up to 1965, 138 were diagnosed at necropsy and 72 by PEG only (Harcourt-Webster and Rack, 1965). Controversy has arisen regarding the function of the corpus callosum, especially when considering the fact that 25 of the 210 reported cases with this defect were neurologically asymptomatic during life and the defect was an accidental finding on necropsy. Along with it goes the fact that attempted

therapeutic surgical division of the commissural pathways in the corpus callosum in epileptics did not cause any untoward effect (van Wagenen and Herren, 1940). However, animal experiments concluded that the function of the corpus callosum is that of supplementing the activity of each hemisphere with information of sensory receptive and sensory integrative processes from the other hemisphere (Meyers, 1965).

The visual evoked potential (VEP) is an electrical discharge measured at the occipital regions, during photic stimulation. Galbraith, Saul, and Gliddon (1969) described patterns of right-left VEP asymmetry in two cases, one with congenital ACC and another with a surgically sectioned corpus. Similar changes were seen in case 1 where stimulation of an insilateral eye produced a smaller potential on the contralateral occipital cortex. The VEP findings support the above-mentioned hypothesis regarding the function of the corpus callosum.

Most authors state that there is no characteristic clinical syndrome which accompanies complete or partial agenesis of the corpus callosum and when neurological symptoms and signs do appear, they are attributed to the coexisting brain anomalies rather than to the callosal agenesis itself. After reviewing the literature, we feel that it is possible to recognize and delineate three main modes of clinical presentation of this anomaly. (1) Failure to thrive, vomiting, and irritability in early infancy. (2) Severe seizure disorder and motor retardation in infancy. (3) Late onset of seizures in childhood or adult age, and/or mental retardation.

Agenesis of the corpus callosum is diagnosed most commonly in infancy and childhood. In the series of Carpenter (1954), 89% of the 19 cases started to manifest initial symptoms during the first 3 years of life. Seizures occurred in 12 of the 19 cases (63%) consisting of various types and were difficult to control. It is obvious also from this series that failure to thrive is as common as seizures (11/19) and that there is a high mortality rate in the infantile age group (Carpenter, 1954). Mental and/or motor retardation are very common and can be observed in most cases. It is of interest that the two sisters presented here, representing the familial occurrence of this syndrome, manifested two different types. The one sib with mild mental retardation and onset of seizures at age seven, and the younger sister with failure to thrive at 6 months of age.

The aetiology of the defect is unknown. Basically, it is considered the result of a localized arrest in neural development.

ACC is not uncommonly associated with other

malformations, such as agenesis of septum pellucidum, porencephaly, hydrocephalus, Dandy Walker cyst, fusion of cerebral hemispheres, polymicrogyria, or heterotopias of grey matter.

Menkes *et al* (1964) described biochemical abnormalities in the brain of a child with hereditary ACC consisting of decrease in lipid content, particularly in the cholesterol and cerebroside fractions and elevation of all amino acids in the cerebrospinal fluid (CSF). In case 1, the CSF showed abnormally high levels of arginine, lysine, and glutamic acid. These abnormalities are not readily explainable by a single enzymatic defect or by an arrest in the chemical changes seen with normal maturation. Therefore, it is more likely that they are the result of profound disturbance of normal metabolism.

The occurrence of agenesis of corpus callosum in sibs, especially offspring of a consanguineous mating, implies strongly that this anomaly may be genetically determined, transmitted by an autosomal recessive gene.

Zellweger (1952) was the first to describe this condition in two brothers, later reported fully by Ziegler (1958). Their parents were not related. They died as infants in status epilepticus and the necropsy revealed total agenesis in both brothers and none in a third brother who died also of status epilepticus.

Naiman and Fraser (1955) reported two sisters with complete ACC who showed severe mental retardation and physical underdevelopment. Their parents were not related. D. H. Jolly, in a personal communication to Naiman observed ACC in both members of a pair of identical twins. Henneaux (1956) reported on two sisters with multiple malformations. One of them had ACC median dysraphism, spina bifida, palato rachischisis, costal fusion, but there are no data on the other. Menkes *et al* (1964) described a family with hereditary partial agenesis which was transmitted as a sex-linked recessive trait. The clinical characteristics were severe intellectual retardation and intractable seizures in two brothers, their half brother, a cousin and a maternal uncle.

Reviewing the familial cases reported, one can conclude that all belong to the infantile types, manifesting the cardinal symptoms of mental and motor retardation or failure to thrive and/or intractable seizures. The presence of those symptoms, separately or in combination, in an infant without a known cause is a clear-cut indication to perform a pneumoencephalogram. This indication is even more justified if there is another case in the family with the symptoms described above or diagnosed as having agenesis of the corpus callosum.

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