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Possible New Autosomal Recessive Syndrome of Partial Agenesis of the Corpus Callosum, Pontine Hypoplasia, Focal White Matter Changes, Hypotonia, Mental Retardation, and Minor Anomalies

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We describe a brother and sister with severe developmental delay, hypotonia, partial agenesis of the corpus callosum, pontine hypoplasia, focal white matter degenerative abnormalities, macrocrania, frontal bossing, deep-set eyes, and hypertelorism. The brother also had Duane syndrome type II and an ectopic right ureter. The coexistence of these multiple physical and brain abnormalities in a brother and sister suggests a new autosomal recessive syndrome with a slowly progressive course. Am. J. Med. Genet. 73:184–188, 1997.© 1997 Wiley-Liss, Inc.

KEY WORDS: atypical corpus callosum partial agenesis; myelination disorders; developmental delay; hypotonia; inborn errors of metabolism; macrocrania; pontine hypoplasia; white matter degeneration

INTRODUCTION

Agenesis of the corpus callosum occurs in complete and partial forms; it has been described as an isolated malformation or associated with other anomalies [Barkovich and Norman, 1988]. In most familial cases, the condition appears to be an autosomal recessive trait, although there are reports of autosomal dominant and of X-linked inheritance [Young et al., 1985]. Agenesis of the corpus callosum may also be seen in some inborn errors of metabolism [Bamforth et al., 1988; Dobyns, 1989; Kolodny, 1989]. In this report, we describe a brother and sister with partial agenesis of the corpus callosum associated with unusual structural abnormalities.

CLINICAL REPORTS
Patient 1

J.W. is the 4-year-2-month-old first-born son of a healthy, nonconsanguineous couple. There was prenatal evidence of a large head, probable agenesis of the corpus callosum, mild right hydronephrosis, and polyhydramnios on ultrasound. There was no teratogenic exposure. He was born at term to a 23-year-old G3P2 white woman by an uncomplicated cesarean section for cephalopelvic disproportion. Apgar scores were 7, 8, and 8 at 1, 5, and 10 minutes, respectively. At birth, he had macrocrania (head circumference [OFC] 37 cm; over 97th centile), weight was 3,487 g (50–75th centile), and length 53.5 cm (90th centile). He was also noted to have microphthalmos, a poor sucking response, and diffuse hypotonia with normal deep tendon reflexes.

At age 1 year, brainstem auditory evoked responses (BAER) showed low amplitude brainstem waveforms suggestive of pontine abnormalities. At age 20 months, a work-up for a protuberant abdomen demonstrated right hydronephrosis. A retrograde pyelogram uncovered a dilated right ectopic ureter entering at the bladder neck. He was diagnosed with left Duane syndrome type II at approximately age 2 and has had bilateral lateral rectus recession.

J.W. has shown significant developmental delays, but no overt neurological deterioration. He sat at 2 years, crawled at 2 1/2 years, and cruised at 3 years but is not yet walking independently. He has spoken many single words but uses only a few words appropriately.

At age 3 9/12 years, J.W. had megalencephaly (OFC 55.7 cm), a height of 105 cm (90th centile), and weight of 16.2 kg (50–75th centile). The skull was plagiocephalic with frontal bossing. The eyes were deep set and he had a left Duane syndrome type II anomaly. He had obvious hypertelorism and telecanthus. There was mild malar hypoplasia (Fig. 1a). There was diffuse

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muscle weakness and hypotonia, which were more marked in the lower limbs. The deep tendon reflexes were diminished.

Head magnetic resonance imaging (MRI) at age 5 months clearly demonstrated an incomplete corpus callosum with hypoplasia of the rostrum, genu, and to a lesser degree the splenium, as well as external hydrocephalus and a somewhat small pons. Head MRI at age 4 years demonstrated better the partial agenesis of the corpus callosum and the absence of cingulate gyrus (Fig. 2a). Probst bundles were present. The frontal and occipital horns of the ventricles were abnormal in shape. The pons was hypoplastic and showed an indentation in the midregion (Fig. 2a). The cerebellum was normal in appearance. Several new areas of high intensity on T2 images on the subcortical white matter of the frontal lobes appeared in the interval since the MRI at 5 months (Fig. 2b). Peripheral nerve conduction studies at age 4 2/12 years were normal. Results of laboratory tests included a normal extended banding karyotype, fragile X DNA status, serum amino acids, urine organic acids, urine mucopolysaccharides and oligosaccharides, lactic acid, ammonia, carnitine, isoelectric focusing of glycoproteins for carbohydrate deficiency glycoprotein disorder, leukocyte lysosomal enzyme studies (including GM1 gangliosidosis, beta-mannosidosis, fructosidosis, alpha-mannosidosis, MPS-VII, Tay-Sachs and variants, metachromatic leukodystrophy, Krabbe disease, Hurler-Scheie syndrome, sialidosis, and sialuria), and very long chain fatty acids. Cerebrospinal fluid (CSF) studies were normal and included protein, oligoclonal bands, IgG levels, lactic acid, and amino acid levels.

**Patient 2**

A.W., a female, is the 3-year-4-month-old only sister of J.W. and was delivered at 37 weeks of gestation. At birth, she had macrocrania (OFC 37.5 cm); her weight was 3,771 g (90th centile) and her length was 54 cm (above 97th centile). Patent ductus arteriosus and mild tricuspid regurgitation were diagnosed by echocardiography and resolved spontaneously. She was also noted to have mild facial asymmetry and decreased truncal tone at birth.

At age 3 years, she had macrocrania (OFC 52.1 cm); her weight was 15.1 kg (90th centile) and her length was 96 cm (75th centile). Her appearance (Fig. 1b) and hypotonia were strikingly similar to her brother’s. A.W. is also developmentally delayed. She rolled over at 8–9 months, sat at 2 1/12 years, crawled at 2 1/2 years, and stood with support at 3 years. The only evidence of possible regression is that by history she stopped standing with support at age 3 3/12 years. She has not yet walked. Her speech is more advanced than that of her brother, and she uses 20–30 understandable words and is beginning to put two words together.

Electroencephalogram and renal ultrasound findings were normal. Head MRI at 12 months clearly showed partial agenesis of the corpus callosum and external hydrocephalus. Head MRI at age 3 4/12 years demonstrated partial agenesis of the corpus callosum which affected the rostrum and genu as well as the splenium.
(Fig. 2c), pontine hypoplasia slightly less severe than that of her brother, and subtle focal subcortical white matter changes (Fig. 2d) which were not present on an earlier MRI. Results of biochemical tests were normal.

The parents had normal appearance and intelligence. Maternal serum amino acids were normal.

**DISCUSSION**

The sibs described here had hypotonia, developmental delay, macrocrania, frontal bossing/plagiocephaly, deep-set eyes, hypertelorism, partial agenesis of the corpus callosum, pontine hypoplasia, focal white matter degeneration, and external hydrocephalus. The brother also has Duane syndrome type II and an ectopic right ureter.

In our patients, the dysgenesis of the corpus callosum is associated with white matter deterioration suggestive of a progressive disorder. Complete agenesis of the corpus callosum leads to a total lack of the corpus callosum, Probst bundles, and associated gyral abnormalities [Barkovich and Norman, 1988]. In cases of partial agenesis of the corpus callosum, the genu, which is formed earlier, is intact, while the splenium and rostrum are not or are incompletely formed. Malformations involving only the genu of the corpus callosum have also been reported [McLeod et al., 1987]. These are thought to be due to destructive lesions of an already developed corpus callosum rather than a true agenesis. In the cases presented, the malformation of the corpus callosum is partial and atypically involves some degree the splenium, rostrum, and genu. Probst bundles and gyral malformations are also present. This pattern of malformation has not been reported previously and cannot be explained by a single early or late insult. Several insults or an ongoing pathological condition occurring during the formation of the corpus callosum are the most plausible explanations. The association between agenesis of the corpus callosum and early progressive inherited disorders [Bamforth et al., 1988; Dobyns, 1989; Kolodny, 1989] indicates that the corpus callosum could be subjected to multiple insults or an ongoing pathological condition during its development. Laboratory investigations for a metabolic cause were unsuccessful. Exposure to a teratogen which could affect the corpus callosum, such as cocaine [Dominguez et al., 1991], was not identified.

Familial syndromes involving agenesis of the corpus callosum which best approximate the findings in this report are summarized in Table I. Most of these syndromes involve mental retardation and hypotonia but also include nonconcordant findings. Published cases of familial agenesis of the corpus callosum are discussed further in Young et al. [1985], and several reports since their review have involved X-linked inheritance patterns [Buntinx and Majewski, 1990; Kang et al., 1992; Proud et al., 1992]. Pontine hypoplasia and focal white matter changes have not been described in previous reports of agenesis of the corpus callosum. Infantile pontine atrophy or hypoplasia has been reported only in association with cerebellar atrophy and has been seen in the carbohydrate-deficient glycoprotein group of syndromes [Barth, 1993; Bawle et al., 1995; Hagberg et al., 1993]. The MRIs of our patients did not demonstrate cerebellar atrophy, and results of carbohydrate-deficient glycoprotein group of syndromes [Barth, 1993; Bawle et al., 1995; Hagberg et al., 1993]. The MRIs of our patients did not demonstrate cerebellar atrophy, and results of carbohydrate-deficient glycoprotein group of syndromes.
coprotein studies were normal. It is interesting to note that pontine hypoplasia is more severe in J.W., who also had an abnormal BAER test suggestive of pontine hypoplasia and Duane syndrome type II. Duane syndrome may be related to cranial nerve anomalies involving the pons [Kowal and McKeown, 1992]. The focal white matter changes seen in these patients are more peripheral than those usually seen in multiple sclerosis and they would be considered even more atypical for adrenoleukodystrophy or Schilder diffuse sclerosis [Valk and van der Knapp, 1989], nonketotic hyperglycemia [Dobyns, 1989], and metachromatic leukodystrophy [Kendall, 1993]. Results of specific laboratory tests for multiple sclerosis, adrenoleukodystrophy, metachromatic leukodystrophy, and nonketotic hyperglycemia were normal. The patients did not have manifestations of Pelizaeus-Merzbacher disease, an X-linked myelin disorder associated with nystagmus, head-bobbing, and visual impairment [Bouloche and Aicardi, 1986]. The diffuse white matter atrophy seen by Lyon et al. [1990] and diffuse white matter hypoplasia seen by Curatolo et al. [1993] were again dissimilar in distribution (see above). A progressive nature is suggested in the children we describe by the focal white matter changes seen after infancy on MRI. Because myelination of the frontal white matter typically takes place by 12 months and may be delayed in infants with developmental problems [Kendall, 1993], the changes on MRI after infancy may reflect this.

This syndrome of partial agenesis of the corpus callosum, pontine hypoplasia, focal white matter changes, macrocrania with external hydrocephalus, and developmental delay in a brother and sister appears to be an autosomal recessive disorder. A progression of mani-
festations is suggested by the comparison of MRIs taken during infancy to those taken as young children. These cases could represent a new syndrome or a more extensive form of one or more previously reported cases or syndromes sharing similar manifestations.

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REFERENCES


