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DEVELOPMENTAL DISORDERS

CAUSES OF CORPUS CALLOSUM DYSGENESIS SYNDROMES

Investigators at the University of Queensland, Brisbane, Australia, and the University of California, Benioff Children's Hospital, studied the clinical features of syndromes associated with agenesis of the corpus callosum (ACC) and their relation to the genetic causes and developmental processes involved. ACC syndromes can be classified by the stage of development primarily affected. Axonal growth continues until 2 months after birth, and structural changes continue post-natally, the thickness of the CC increasing anteriorly through childhood and posteriorly during adolescence. Early perturbations of CC development (weeks 14 and 15 post conception) result in complete agenesis, and later developmental disturbances (weeks 18 and 19) result in partial agenesis confined to the posterior CC. ACC can occur with disorders of neuronal and/or glial proliferation, telencephalic midline patterning, and axonal growth or guidance, similar to that observed in the mouse model. Copy number variations (e.g. 1q42-q44 deletion) and single gene mutations are present in some ACC syndromes, but a clear genetic cause is not identified in the majority. Neuroimaging has extended the number and variety of syndromes recognized in association with ACC and these include the major ciliopathies: Joubert syndrome (molar tooth sign, vermis hypoplasia); Meckel syndrome (occipital encephalocele, absence of olfactory bulbs); hydrolethalus syndrome (severe hydrocephalus); acrocallosal syndrome (exencephaly, hydrocephalus); Bardet-Biedl syndrome (molar tooth sign, retinitis pigmentosa). (Edwards TJ, Sherr EH, Barkovich J, Richards LJ. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. **Brain** 2014 Jun;137(Pt 6):1579-1613).

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COMMENTARY. This review provides a comprehensive classification of the clinical and genetic features of syndromes associated with callosal agenesis. In a clinical reference guide to neurological syndromes [1], among approximately 250 syndromes listed, 18 have an associated CC dysgenesis. Seizures, especially infantile spasms, as in Aicardi syndrome, are an established complication of ACC whereas behavioral and cognitive impairments as isolated deficits are less well documented.

ACC and autism. About one third of a group of 26 adults with ACC presented with autism whereas in childhood only 3 of the group had met criteria for a diagnosis of autism spectrum disorder [2]. Parent ratings of childhood behavior indicate that children with agenesis are less likely to be autistic but as adults ACC is a risk factor for developing autism. Both genetic and environmental factors may be involved in the cause of ACC and its autistic features.

References.

1. Millichap JG. Neurological Syndromes : A Clinical Guide to Symptoms and Diagnosis. New York: Springer; 2013:279.
2. Paul LK, et al. Brain. 2014 Jun;137(Pt 6):1813-29.

NEUROPSYCHOLOGICAL AND LANGUAGE DEFICITS IN 22q11.2 DELETION SYNDROME

Investigators at Bambino Genu Children's Hospital, Rome, and multiple additional centers in Italy conducted a retrospective and prospective study of clinical manifestations at diagnosis and during follow-up of 228 patients with 22q11.2 deletion syndrome. Clinical diagnosis, confirmed by cytogenic or molecular analysis, was made before 2 years of age in 71% of patients. Median age at diagnosis was 4 months (range 0 to 36 years 10 months). Early diagnosis was predominantly related to heart anomalies and neonatal hypocalcemia. In patients diagnosed after 2 years of age, speech and language impairment, developmental delay and facial features were the main diagnostic elements. During follow-up, the frequency of autoimmune manifestations (P=0.015) and speech disorders (P=0.002) increased. Psychomotor and speech/language developmental delay were reported in 48% and 53% cases, respectively, leading to the diagnosis in subjects older than 2 years. Orthopedic abnormalities, mainly scoliosis and congenital clubfoot, were observed in 78 of 217 patients. (Cancrini C, Puliafito P, Digilio MC, et al. Clinical features and follow-up in patients with 22q11.2 deletion syndrome. **J Pediatr** 2014 Jun;164(6):1475-1480.e2).

COMMENTARY. The syndrome 22q11.2 deletion, also known as DiGeorge (DGS), velo-cardio-facial (VCFS), cono-truncal-anomaly-face (CTAF), Shprintzen, Strong, Sedlackova, Cayler cardiofacial, and congenital thymic aplasia syndromes, is of interest particularly to the cardiologist in patients presenting in early infancy. In children older than 2 years, the neurologist is consulted because of speech and language delay and psychomotor behavioral disorders. Symptoms of hypocalcemia may complicate heart anomalies in the neonatal period and behavioral disorders in older children. Patients of all ages share the characteristic dysmorphic features of hypertelorism, broad nose tip, small mouth, and ear anomalies. The main presenting features of 22q11.2 deletion syndrome vary with the patient's age [1]. The mnemonic, CATCH-22 is often applied to the