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CONGENITAL MALFORMATIONS

SMITH-LEMLI-OPITZ SYNDROME

Two sibs, a male aged 3 years and female aged 7 months, with a variant of Smith-Lemli-Opitz (SLO) syndrome and atypical sterol metabolism are reported from the Kennedy Krieger Institute, Johns Hopkins University, Baltimore, MD. Physical and developmental abnormalities, including microcephaly, ptosis, low-set ears, triangular face, toe syndactyly, growth and mental retardation, were mild but characteristic of SLO syndrome. Plasma cholesterol levels were only mildly depressed, and the expected increase in plasma levels of 7-dehydrocholesterol (7DHC) was less than that found in classical SLOS. The parents' sterol metabolism was abnormal compared to other SLOS parents, with markedly elevated 7DHC in their lymphoblasts. (Anderson AJ, Stephan MJ, Walker WO, Kelley RI. Variant RSH/Smith-Lemli-Opitz syndrome with atypical sterol metabolism. Am J Med Genet Aug 1998;78:413-418). (Respond: Richard I Kelley MD, PhD, Kennedy Krieger Institute, 707 North Broadway, Baltimore, MD 21205).

COMMENT. For those readers, like me, confused by the authors' RSH prefix appellation for Smith-Lemli-Opitz syndrome (SLOS), unidentified in the text, my colleagues in genetics (Joel Charrow and Teri Hadro) explain that the RSH designation, attributed to Opitz, is based on the initials of the first three patients reported with the syndrome, unrelated boys with mental retardation and facial, limb, and genital anomalies.

SLOS is an autosomal recessive disorder, occurring in 1/20,000 births, and manifested by infantile feeding difficulties, vomiting, and failure to thrive, multiple congenital anomalies of the central nervous system, heart, kidneys, and lungs, polydactyly and syndactyly, cleft palate, facial dysmorphisms, genital anomalies, and mental and growth retardation. Some 30 years after the initial description of SLOS (1964), Tint and colleagues discovered an inborn error of cholesterol biosynthesis in patients with classical SLOS (1994), and correlated the severity and outcome with plasma sterol levels among variants of the syndrome (1995). An inherited enzymatic deficiency of 7-dehydrocholesterol-reductase results in hypocholesterolemia and increased levels of 7DHC in plasma. This

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The editor is Pediatric Neurologist at Children's Memorial Hospital and Northwestern University Medical School, Chicago, Illinois.
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biochemical marker for the syndrome has permitted early diagnosis in mildly affected members of a family, leading to treatment with dietary cholesterol replacement, improvement in growth, and control of hyperactivity and other behavioral problems. Pediatricians and pediatric neurologists should have an increased awareness of the variability in the severity of manifestations of SLOS. The diagnosis should be considered in children with unexplained mental retardation or psychomotor delay, especially in those with toe syndactyly, other minor congenital anomalies, and an early history of failure to thrive. Noonan's syndrome is one misdiagnosis reported. Of interest is the frequency of hyperactive behavior in children with SLOS; a child in one report was first diagnosed with ADHD and benefited from treatment with methylphenidate. A normal plasma cholesterol determination does not rule out the diagnosis of SLOS, and measurement of 7-DHC is necessary in suspected cases.

Three articles and reports of cases of SLOS from three different countries, appearing in the current literature, point to the increased interest in the syndrome and its prior lack of recognition. In addition to the two patients reported from Johns Hopkins, three related patients with mental retardation and minimal physical signs are reported from McMaster University, Hamilton, Ontario, Canada (Nowaczyk MJM, Whelan DT, Hill RE. Smith-Lemli-Opitz syndrome: Phenotypic extreme with minimal clinical findings. Am J Med Genet Aug 1998;78:419-423), and three cases of varying severity are analysed genetically at the University of Amsterdam, The Netherlands (Waterham HR, Wijburg FA, Hennekam RCM et al. Smith-Lemli-Opitz syndrome is caused by mutations in the 7-dehydrocholesterol reductase gene. Am J Hum Genet Aug 1998;63:329-338).

FORAMINA PARIETALIA PERMAGNA SYNDROME

A boy, born with a soft cranium, had symmetrical defects in the parietal bones, small head, triangular face, micrognathia, small mouth, downslanted palpebral fissures, arched eyebrows, short webbed neck, branchial fistulae, and sensorineural deafness. This case-report from the Children's Memorial Health Institute, Warsaw, Poland, and the Royal Alexandra Hospital for Children, Sydney, Australia, represents a unique branchio-oto syndrome with skeletal abnormalities including foramina parietalia permagna. (Chrzanowska K, Kozlowski K, Kowalska A. Syndromic foramina parietalia permagna. Am J Med Genet Aug 1998;78:401-405). (Respond: Dr Kazimierz Kozlowski, New Children's Hospital, PO Box 3515, Parramatta, New South Wales 2124, Australia).

COMMENT. My colleagues in radiology, who were familiar with the coincidental and occasional finding of large symmetrical posterior parietal skull defects in skull X-rays, referred me to Theodore Keats' "Atlas of Normal Roentgen Variants," (Chicago, Year Book Med Publ, 1988). "Foramina parietalia permagna" may occur sporadically, as an inherited dominant trait, or as part of various branchial syndromes. The authors conclude that this case report represents a new branchial syndrome.

In an editorial comment (Syndromal foramina parietalia permagna: "New" or FG syndrome? Comments on the paper by Chrzanowska et al. (1998). Am J Med Genet Aug 1998;78:406-407), Rauch A, Opitz JM, and Walker D opine that, based on our extensive recent experience, the patient has the FG syndrome, an X-linked recessive syndrome of multiple congenital abnormalities and mental retardation, as described by Opitz and Kaveggia in 1974 . However, the Chrzanowska syndrome emphasizes the parietal bone defects and branchial arch fistulae, anomalies that appear to be absent in all but one of the FG syndrome cases. Perhaps the appellation, Opitz-Chrzanowska (OC) syndrome would be a more appropriate