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Macrocephaly Syndromes

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Anatomic megalencephaly resulting in macrocephaly occurs in more than 100 multiple congenital anomaly syndromes. A number of macrocephaly syndromes show accompanying somatic overgrowth, but some show normal somatic growth. This discussion provides a review of several macrocephaly syndromes that might be encountered by the pediatric neurologist. Growth patterns, craniofacial features, congenital anomalies, central nervous system imaging findings, performance, and mode of inheritance for each condition are reviewed as well as recent developments in the molecular genetic testing for these conditions.
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Megalencephaly, defined as a brain weight/volume ratio greater than the 98th percentile for age (or ≥2 standard deviations [SD] above the mean), results from true hyperplasia or overproduction of central nervous system (CNS) parenchyma.[1] The actual prevalence is unknown. Megalencephaly is generally accompanied by macrocephaly, an occipitofrontal circumference (OFC) greater than the 98th percentile. However, macrocephaly may occur in the absence of megalencephaly because of underlying hydrocephalus, cerebral edema, neoplasia, fluid collection, or thickened calvarium. Megalencephaly is divided into an anatomic type (developmental) and a metabolic type. Metabolic megalencephaly refers to various storage and degenerative encephalopathies and will not be discussed here. Anatomic megalencephaly most often occurs as an isolated clinical finding, as in benign familial megalencephaly. However, it occurs as part of a broad pattern of anomalies and dysmorphic features in many different syndromes, referred to as syndromic megalencephaly. In the clinical genetics and dysmorphology literature, the terms macrocephaly and megalencephaly are typically used interchangeably, with the assumption that nonmegalencephalic etiologies of macrocephaly have been excluded. Well over 100 syndromes with macrocephaly are known, and some of these are quite rare. This discussion will review several relatively common megalencephaly-associated macrocephaly syndromes that might be encountered by pediatric neurologists (Table 1). Not included here are multiple congenital anomaly syndromes caused by rare chromosomal aberrations, skeletal dysplasias, and syndromes with only relative macrocephaly (OFC of normal size for age but large in proportion to small stature).[1]

Macrocephaly caused by anatomic megalencephaly is usually apparent at birth, and postnatal head size continues to be large, growing at a rate parallel to the upper percentiles. In some syndromes, increased OFC may be the presenting sign. Thus, the evaluation of any child with macrocephaly should begin with a detailed history, including family, developmental, and growth history, and an examination for evidence of dysmorphic features or anomalies. In syndromic macrocephaly, a variety of gyral and structural CNS anomalies occur, and neuroimaging studies are important in the identification of specific abnormalities. However, the diagnosis of the underlying syndrome in these individuals rests largely on the associated manifestations. As a result, a careful search for other congenital anomalies should be undertaken, including abdominal ultrasonography, echocardiogram, osseous survey, and ophthalmologic examination. As indicated, appropriate cytogenetic studies and, if available, molecular genetic studies should be performed.[1]

Macrocephaly Syndromes With Prenatal and/or Postnatal Somatic Overgrowth

Overgrowth syndromes frequently feature macrosomia accompanied by megalencephaly, presumably because of a common etiology causing excessive growth of many different tissue types. In addition to macrocephaly, overgrowth syndromes often share developmental delay, hypotonia, and in-

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Table 1 Macrocephaly Syndromes: A Sampling

	Gene	Inheritance
Macrocephaly syndromes with overgrowth		
Sotos	*NSD1*	AD, mostly sporadic
Simpson-Golabi-Behmel	*GPC3*	XLR
Fragile X	*FMR1*	XLR
Weaver	Unknown	AD, mostly sporadic
M-CMTC	Unknown	All sporadic
Bannayan-Ruvalcaba-Riley	*PTEN*	AD
Macrocephaly syndromes without overgrowth		
FG	*MED12*	XLR
Greig cephalopolysyndactyly	*GLI3*	AD
Acrocallosal	Unknown	AR
Gorlin	*PTCH*	AD

AD = autosomal dominant; XLR = X-linked recessive; AR = autosomal recessive.

creased risk of neoplasia. The distinguishing dysmorphic features, associated malformations, family history, and specific growth patterns characteristic of each syndrome contribute to the clinician's recognition of these relatively rare conditions.

Sotos Syndrome

Sotos syndrome (cerebral gigantism) is a relatively common overgrowth syndrome reported in more than 300 individuals. Macrocephaly of prenatal onset is present in 50% of individuals and in 100% by 1 year of age. Head circumference is typically well above the 97th percentile. Prenatal somatic overgrowth, particularly affecting length, results in a mean term birth length of 55.2 cm and birth weight of 3.9 kg. Postnatal overgrowth persists during childhood, but by adulthood height may normalize. Advanced bone age occurs in 84% of children with Sotos syndrome.[2-5]

The craniofacial features are particularly characteristic between 1 and 6 years of age and include high forehead with frontal bossing, sparse hair in the frontoparietal region, downslanting palpebral fissures, apparent hypertelorism, long narrow face, prominent mandible, and malar flushing (Fig 1). A high narrow palate, premature eruption of teeth, and large hands and feet are commonly present. Congenital heart defects, strabismus, nystagmus, optic disc pallor, retinal atrophy, cataracts, glaucoma, and iris hypoplasia are occasional findings.[2-5] There is an increased risk for neoplasia, with about 3.9% of individuals showing tumors, including Wilms tumor, hepatocellular carcinoma, neuroblastoma, vaginal epidermoid carcinoma, small cell carcinoma of the lung, sacrococcygeal teratoma, giant cell granuloma of the mandible, and acute lymphocytic leukemia.[5]

Hypotonia, poor coordination, and speech delay are common, and the great majority of individuals show mild to severe mental retardation. IQs range from 40 to 129, with a mean of 78.[6] Significant behavioral abnormalities are common; large size and clumsiness contribute to difficulty with peer relationships and social adjustment.[3,4] Approximately 25% of individuals with Sotos syndrome develop seizures, including absence, tonic-clonic, myoclonic, and partial complex seizures.[3]

Schaefer and coworkers[7] described a characteristic pattern of neuroimaging findings in individuals with Sotos syndrome

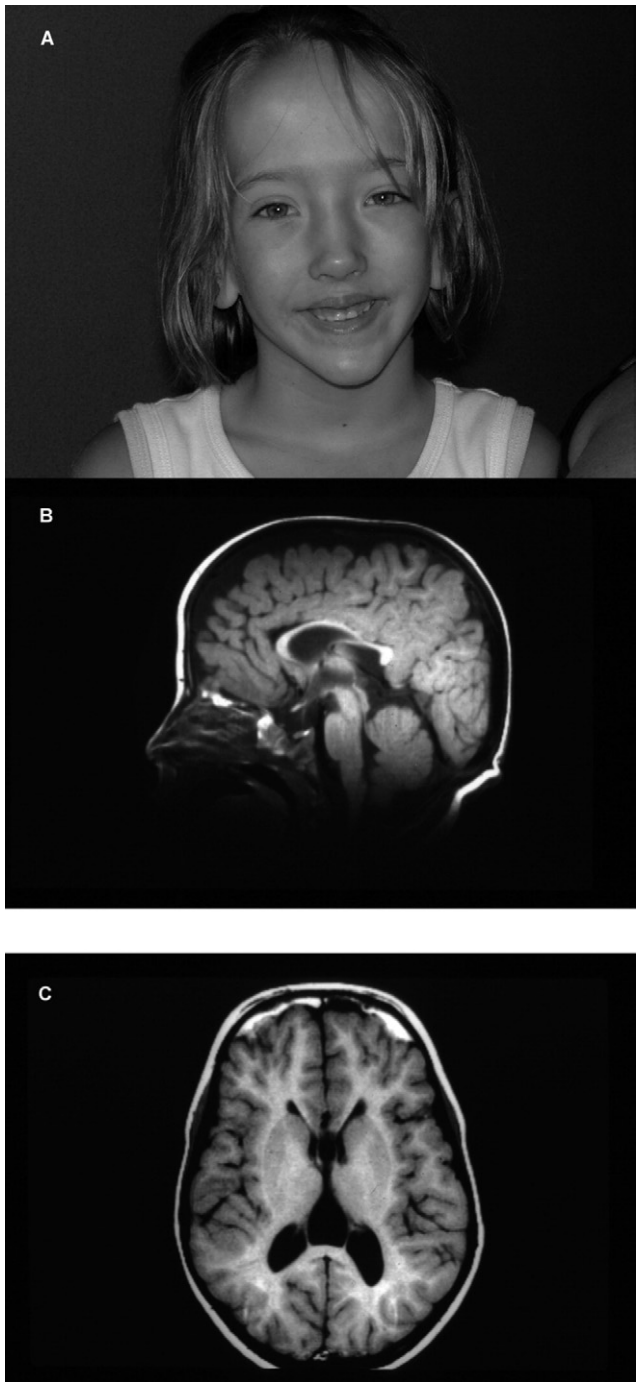

Figure 1 Sotos syndrome. (A) Typical craniofacial features of syndrome. (B) Sagittal T1 magnetic resonance imaging in Sotos syndrome. Note the increased extra-axial fluid and thin corpus callosum. (C) Axial T1 magnetic resonance imaging in Sotos syndrome. Note the cavum septum pellucidum, cavum vergae, and enlargement of the ventricles in the trigone region.