Beckwith–Wiedemann syndrome in a child with Chiari I malformation

Case report

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The authors present the case of a child diagnosed as having Beckwith–Wiedemann syndrome and Chiari I malformation. Hemihypertrophy is associated with Beckwith–Wiedemann syndrome and has been described in conjunction with Chiari I malformation. The authors hypothesize that the hemihypertrophy that may involve the skull base and Chiari I malformation found in their patient are not spurious findings but are pathologically related, perhaps by slight dysmorphologies of the posterior cranial fossa.

Key Words • hemihypertrophy • overgrowth syndrome • hindbrain • pediatric neurosurgery

Beckwith–Wiedemann syndrome is a rare disorder with the cardinal features of exophthalmos, macroglossia, and gigantism in the neonate. Visceromegaly, adrenocortical cytomegaly, abdominal wall defects, and dysplasia of the renal medulla are other features commonly found in BWS. Furthermore, patients with BWS are at an increased risk of harboring specific tumors such as adrenal carcinoma, nephroblastoma, hepatoblastoma, and rhabdomyosarcoma. The incidence of BWS is unknown; however, Thorburn, et al., have found an estimated incidence of one in 13,700 births. The mode of inheritance is complex. Possible patterns include autosomal-dominant inheritance with variable expressivity, contiguous gene duplication at 11p15, and genomic imprinting resulting from a defective or absent copy of the maternally derived gene. Hemihypertrophy is also often reported in BWS. We have reported a potential association between hemihypertrophy and Chiari I malformation. We now report on a child with BWS with hemihypertrophy as a component in addition to Chiari I malformation.

Case Report

This 3-year-old girl was born at full gestation to non-consanguineous parents. At birth she was hypoglycemic. The child was initially noted to have overgrowth and hyperpigmentation of the skin. The overgrowth was isolated to the right lower extremity. Focalities on her physical examination included mild facial asymmetry, mild hypertelorism with slanted palpebral fissures, macroglossia, clinodactyly of the fifth digits, mild exophthalmos, and slightly decreased muscle tone. The child was seen in our clinic following the discovery of a Chiari I malformation on diagnostic MR imaging (Figs. 1 and 2). She is currently asymptomatic from her hindbrain hernia.

Discussion

Congenital hemihypertrophy, as seen in our patient, can occur as a single finding or as part of a spectrum in many syndromes such as BWS, Proteus, Weaver, Marshall–Smith, Sotos, Simpson–Golabi–Behmel, Klippel–Trenaunay–Weber, neurofibromatosis Type 1, and CMTC syndromes. One theory attributes CMTC to a failure of development of the mesodermal vessels in the early embryonic stage; more—and to be discussed later—Chiari I malformation has been suggested by some to originate in a mesodermal defect. Of note, a variation termed macrocephaly CMTC was reported by two different authors and was found to have an associated Chiari I malformation. Interestingly, we have shown that neurofibromatosis Type 1, often associated with hemihypertrophy, has an increased rate of Chiari I malformation associated with it.

Hemihypertrophy has been subclassified into complex, simple, and hemifacial hemihypertrophy. Complex hemihypertrophy involves the majority of half of the body and may involve parts on the same side (complex ipsilateral hemihypertrophy).
hemihypertrophy) or both sides. Simple hemihypertrophy involves a single extremity, and hemifacial hypertrophy involves one side of the face. The cause of isolated hemihypertrophy is not known, although it has been argued that Proteus syndrome can result from somatic mutation, giving rise to cell lines with abnormal growth patterns. Molecular studies have suggested that failure of growth regulation may be the culprit in BWS and Simpson-Golabi-Behmel syndrome. Allelic mouse mutations that cause skeletal overgrowth have been found to involve the natriuretic peptide receptor C gene (Npr2). In a study of 53 affected children, Carlin, et al., suggested that hemihypertrophy is an underappreciated diagnostic clue for BWS in the relatives of probands. Chitayat, et al., postulated that the cellular hypertrophy seen in patients with BWS and Chiari I malformation may not be spurious but rather may be underappreciated, on the basis of this case study and other reports regarding hemihypertrophy and Chiari I malformation.

Our current case and our previously unreported cases involved both a Chiari I malformation and BWS. The cause of Chiari I malformation is not known, although many reports have indicated that a defect of posterior fossa mesoderm (the occipital bone is derived from the chondrocranium, a cartilaginous precursor) may yield a cavity that is not capacious enough to house the developing hindbrain and thus predisposes one to tonsillar ectopia (that is, the Chiari I malformation). Nishikawa, et al., specifically found that both the exocciput (aspect of the occipital condyle inferior to the superior portion of the jugular tubercle) and supraocciput (internal occipital protuberance to the opisthion) were underdeveloped in this group, although rhombencephalic derivatives developed normally. Several authors have found no difference, however, in the size of the posterior fossas in some patients with tonsillar ectopia compared with those of controls. In addition, a Chiari I malformation has been speculated to be more common in Crouzon syndrome because of a posterior fossa compromised by lambdoidal synostosis.

Lapresle, et al., have reported on a case of upper-left and lower-right muscular hypertrophy in a patient with syringomyelia and Arnold–Chiari malformation. The delineation of what type of Arnold–Chiari was not mentioned, however, although presumably it represents a Chiari I malformation because the patient’s photographs depict a standing individual with good muscle bulk in the lower extremities (which would be unusual if this were a patient with the Chiari II malformation). Interestingly, Caldemeyer, et al., report on a patient with hypophosphatemic rickets and Chiari I malformation and hypothesize that overgrowth of the posterior fossa necessitated egress of the cerebellar tonsils from within the posterior fossa and into the cervical subarachnoid space. We have shown that the posterior fossa volume is significantly less in patients with rickets and those with rickets with Chiari I malformation. Are slight hypertrophies of the cranium present in patients with overgrowth syndromes, as in our patient with BWS without facial involvement? Could slight overgrowth of the posterior fossa in our patients without facial hemihypertrophy predispose them to hindbrain herniation? These notions can be entertained and would shed light on the seemingly higher rate of Chiari I malformation in patients with hemihypertrophy. Conversely, atypical hemifacial microsomia has been associated with Chiari I malformation with syringomyelia in at least two cases. Perhaps the current nomenclature used to describe hemihypertrophy must go beyond the inclusion of facial hypertrophy alone and include morphometrics of the skull base.

We hypothesize that the association between BWS and Chiari I malformation may not be spurious but rather may be underappreciated, on the basis of this case study and other reports regarding hemihypertrophy and Chiari I malformation. Our hopes are that by knowing the genetics of one disease (for example, BWS), these data will shed light on potential genetic links to Chiari I malformation.

References


Manuscript received June 21, 2004.
Accepted in final form February 9, 2005.

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