

Identical Twins With Weissenbacher-Zweymüller Syndrome and Neural Tube Defect

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Neurologic abnormalities have been described only once previously in a child with Weissenbacher-Zweymüller syndrome (WZS), a rare skeletal dysplasia, evident neonatally. We report on identical twin male infants with skeletal findings typical of WZS, including small size at birth, proximal limb shortness, mid face hypoplasia, and myopia. In addition, twin B had a parieto occipital encephalocele while twin A had a meningocele at the same location. Twin B has had significant delays in development and hearing loss.

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INTRODUCTION

In 1964, Weissenbacher and Zweymüller described a child with Robin sequence, rhizomelic chondrodysplasia with bowing of the femora, and coronal clefts of the vertebral bodies. Haller et al. [1974], Maroteaux et al. [1970], Cortina et al. [1977], Scribanu et al. [1987], and Galil et al. [1991] each identified this disorder in children who showed remarkable improvement in growth rate after ages 2 to 3 years and eventually had normalization of radiographic peculiarities. Several authors have also described families in which there are individuals with skeletal and eye changes similar to those found in the Stickler and Marshall syndromes but also overlap with Weissenbacher Zweymüller syndrome [Winter et al., 1983; Kelly et al., 1982]. Autosomal dominant inheritance is suggested in these families. Homology between the Sticker and Weissenbacher-Zweymüller syndromes (WZS) was proposed based on these observations. However, recently Chemke et al. [1992] reported five pa-

tients in detail from three families who did not have manifestations compatible with Stickler syndrome nor did relatives. These authors along with Galil et al. [1991] suggested that the distinguishing phenotypic changes of WZS include short stature with rhizomelic proportions at birth, improvement in growth after age 3 years, lack of joint deformity in later childhood, and autosomal recessive inheritance.

Abnormalities of brain structure were not present in any of the children with the exception of an infant reported by Dinno et al. [1976] who had hydrocephalus and a small occipital encephalocele. This individual also had other abnormalities which are not typical of WZS and may have a separate, but radiographically similar, disorder.

We describe identical male twins with small size at birth, midface flatness, prominent eyes, brachycephaly, and rhizomelic proportions with radiographic abnormalities consistent with WZS. Twin B had a large, high parietal-occipital meningoencephalocele, while a small meningocele was identified by MRI scan at a similar site in Twin A. These twins provide evidence that central nervous system abnormalities may be associated with the WZS.

CLINICAL REPORT

These male identical twins were born after an uncomplicated 37 week gestation to a healthy, unrelated couple who were both 26 years old at the birth of these infants. This was their second pregnancy; the first ended in a spontaneous loss at 12 weeks gestation. There have been no subsequent children. Neither parent is known to have myopia, hearing loss, or arthritis.

Twin A

Twin A presented in vertex position and delivered without complications. Birth weight was 2.0 kg (<5th centile), length was 48 cm (10th centile), and head circumference (OFC) was not recorded. There were no problems immediately after birth. Apnea and bradycardia monitoring was instituted because of significant apnea and an abnormal pneumogram in Twin B. Alarms were never recorded in Twin A; a pneumogram was normal.

At age 2 months, length was 57 cm (<5th centile), weight was 4.0 kg (10th centile), and OFC was 35.5 cm (less than the 2nd centile). Craniofacial findings were

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Fig. 1. Full view of Twin A; proximal limb shortening is evident as is severe mid-face hypoplasia, short up-turned nose, and prominent eyes.

virtually identical to those of his brother with peculiarities including midfacial hypoplasia, prominent eyes, downturned orbital ridges, short, upturned nose, mild micrognathia, and downturned mouth (Fig. 1). Large anterior and posterior fontanelles were noted with mild widening of the sagittal and lambdoidal sutures. Scaphocephaly and a midline bony defect in the posterior parietal region were present on radiographs with a small meningocele demonstrated by MRI scan. Long bone and vertebral abnormalities were identical to those described for Twin B.

Ophthalmologic evaluation showed severe myopia (-14.00 diopters bilaterally) with poorly developed, hypopigmented fovea, and macula. Visual acuity could not be accurately assessed at age $2\frac{1}{2}$ years, but it was estimated to be 20/200 or better. He could distinguish the identity of individuals at a distance of 100 m and followed small objects well.

Growth proceeded at a normal rate through age 3 years, but height remained below the 5th centile and OFC below the 2nd centile. Proximal limb shortening was persistent. Development of fine and gross motor skills has been within the broad range of normal. Expressive language acquisition was mildly delayed. Hearing has not been assessed recently, but brain stem auditory evoked potential testing in infancy was normal.

Twin B

Twin B presented in the breech position and required immediate intubation for failure to initiate respirations. He was described as "shocky," with severe anemia re-



Fig. 2. Face of Twin B at 2 months; craniofacial findings are very similar to those of his brother. Encephalocele is obvious.

quiring immediate transfusion. Weight was 2.02 kg (<5 th centile) and length was 47 cm (5th centile). OFC was not recorded; a large cephalohematoma in the occiputo-parietal area was noted. Proximal limb shortness was evident. The infant was extubated at 24 hours but remained hospitalized for 10 days because of recurrent apnea and bradycardia. At 2 weeks, the infant was readmitted to the hospital for treatment of *E. coli* meningitis.

At 2 months, this infant weighed 3.7 kg (5th centile), length was 51 cm (<5 th centile), and OFC was 36 cm (2nd centile). Phenotypic peculiarities were striking and included shallow orbits, prominent eyes, short upturned nose with elongated philtrum, mild micrognathia, and down-turned upper lip (Figs. 2–4). Ear form and placement were normal. Anterior fontanelle was 5×5 cm. A large, protruding, fluid-filled mass which transilluminated brightly was present over the parieto-

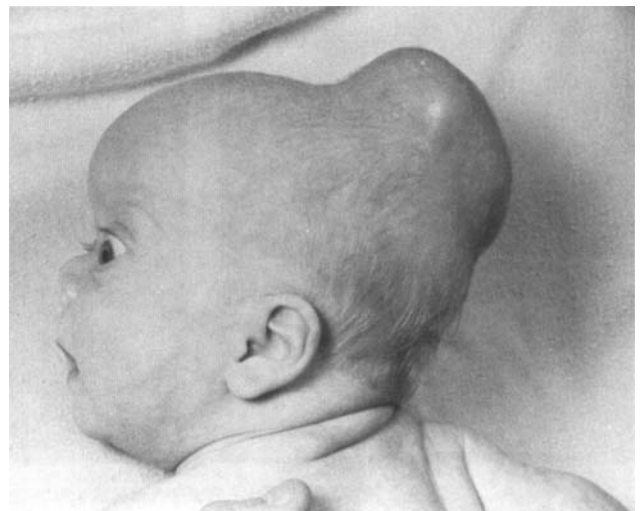


Fig. 3. Twin B, right lateral view to show large high parieto-occipital encephalocele and severe mid-facial hypoplasia.

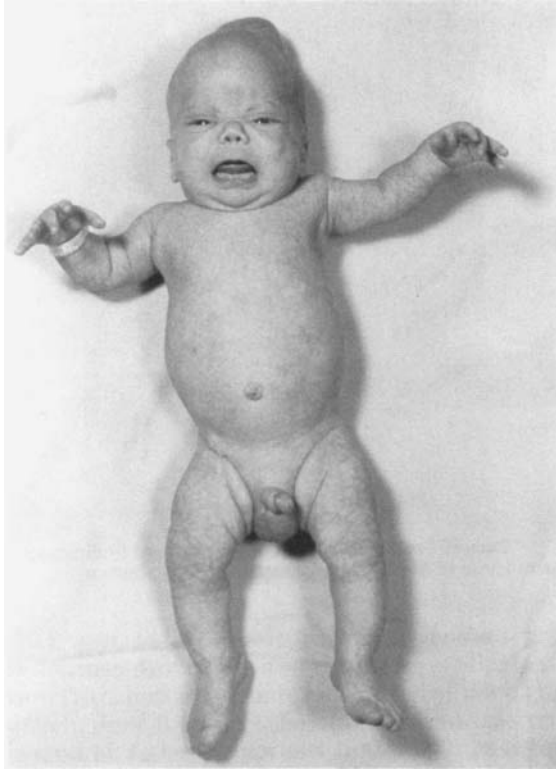


Fig. 4. Full view of Twin B also shows proximal limb shortness.

occipital region. Subsequent MRI scan showed this to be a meningo-encephalocele which communicated with the dilated left lateral ventricle (Figs. 5, 6). The right lateral and third ventricles were also large and the corpus callosum was thin. Skeletal exam documented

mild flare of the ribs, proximal limb shortness, small hands, and feet with hypoplasia of the nails of the 4th and 5th fingers of both hands. Skull radiographs showed frontal bossing and a protruberant parieto-occipital region with associated soft tissue mass. Long bone findings included narrow diaphyses and bulbous metaphyses particularly notable in the femora (Fig. 7). There was incomplete coronal and sagittal clefting of the 4th and 5th lumbar vertebral bodies and mild platyspondyly (Fig. 8).

A ventriculo-peritoneal shunt was placed to decompress the ventricles. Surgical repair of the encephalocele was planned for age 4 or 5 years. Several revisions of the shunt have been necessary to deal with malfunction or to treat infection.

Ophthalmologic exam disclosed high myopia (-16.00 diopters in each eye) with a poorly defined, hypopigmented fovea and macula. At age 3 years, visual acuity was estimated to be 20/100 or slightly better with spectacle correction.

A right hemiparesis evolved during the first year of life. Exam at age 3 years showed mildly increased neurologic tone in the right arm and leg most evident when the child ran. Expressive speech was estimated to be at a functional level of 24 to 27 months at chronologic age 36 months. Gross and fine motor skills were assessed at about 30 months level. Testing by brain stem auditory evoked potential and sound field evaluation detected 60 Db hearing loss bilaterally; hearing aides were prescribed. Length continued to grow just below the 5th centile and proximal limb shortness was still apparent at age 3 years.

Because of the presence of midline cerebral defects, thyroid function and cortisol secretion were assessed by provocative testing and found to be normal.



Fig. 5. MRI scan of Twin B at 2 1/2 mos of age; large encephalocele connecting with the dilated left lateral ventricle is evident as is enlargement of the right lateral and third ventricles.

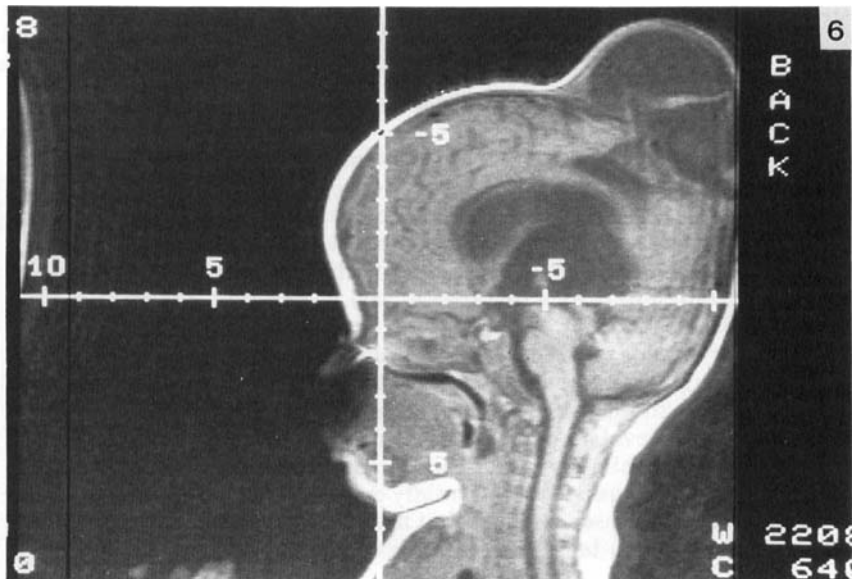


Fig. 6. Sagittal MRI view of Twin B with evidence of encephalocele and disruption of surrounding neural tissue.



Fig. 7. Radiograph of the femurs of Twin B. The diaphyses are narrowed, and metaphyses are bulbous.



Fig. 8. Lateral radiograph of the spine of Twin B to show mild platyspondyly and incomplete clefting of the 4th and 5th lumbar vertebral bodies.

DNA Fingerprinting Studies

The genetic makeup of the sibs was verified at two highly polymorphic chromosomal loci. Genomic DNA was extracted from lymphocytes, Southern blotted, and hybridized to variable number tandem repeat probes, D15S24 and D15S86. D15S24 has been localized close to the centromere, and D15S86 near the telomere. They are sufficiently distant to be considered unlinked. Both sibs were found to be heterozygous for identical alleles at D15S86 and D15S24 (results not shown). These data strongly support monozygosity, since it is much less likely that a pair of dizygotic offspring would inherit this configuration of alleles ($P = 0.0625$).

DISCUSSION

Weissenbacher-Zweymüller syndrome is defined primarily by the presence of characteristic roentgenographic findings in infancy combined with micrognathia, U-shaped cleft palate and posteriorly placed tongue, the Robin sequence. Skeletal abnormalities consist of metaphyseal widening, especially prominent in the femora (leading to a "dumbbell" shape), micrognathia, and, in some patients, incomplete coronal clefting of the lumbar vertebral bodies [Weissenbacher and Zweymüller, 1964; Maroteaux et al., 1970; Haller et al., 1974; Cortina et al., 1977; Scribanu et al., 1987; Galil et al., 1991; Chemke et al., 1992]. We believe that the

findings noted in the twins we report fit quite well within this phenotype.

The craniofacial and ophthalmologic abnormalities vary widely among the families currently accepted to have WZS. Our patients have severe mid-face hypoplasia, a small, upturned nose, and significant myopia similar to the findings in the patients reported by Scribanu et al. [1987], Galil et al. [1991], Kelly et al. [1982], and Winter et al. [1983]. The twins also had hypopigmentation of the retina with a poorly defined macula, a finding not previously observed. Kelly et al. [1982] and Winter et al. [1983] independently suggested that their patients with severe myopia and glaucoma had the Stickler/Marshall syndrome and, further, that WZS represents a neonatal expression of the Stickler syndrome based on the overlap of craniofacial and ophthalmologic findings. Scribanu et al. [1987] described another child with severe glaucoma and high myopia whose skeletal features suggested WZS. She concluded that WZS may fit within a continuum of hereditary arthro-ophthalmopathies. In a recent comprehensive review of the syndrome, Chemke et al. [1992] suggest that WZS is unique, citing similarity of phenotype in the reported patients, characteristic roentgenographic findings, and, most importantly, the achievement of normal body proportions and radiographic appearance of bone with time. These authors do not consider myopia a usual

component of WZS. Ultimate resolution of the controversy regarding the overlap of WZS and Stickler syndrome will await further linkage studies of these disorders. There is evidence of linkage to the type II procollagen gene on chromosome 12 for at least some families with Stickler syndrome [Knowlton et al., 1989] but there is no linkage data available for families with WZS.

Our patients provide evidence for additional phenotypic variation in WZS. None of the previously reported children currently considered to have this syndrome had abnormalities of brain structure or significant psychomotor retardation apart from expressive language delay in individuals with hearing loss. Several children had delays in early motor skill acquisition but were functioning in the normal or near normal range in the late preschool period [Scribanu et al., 1987; Galil et al., 1991; Chemke, et al., 1992]. An infant with a small occipital encephalocele and hydrocephalus, reported by Dinno et al. [1976], was initially diagnosed to have WZS. The radiographic findings in this child included generalized platyspondyly, short horizontal ribs, broad ilial wings, and flat pubic bones. The child also had "slit-like" palpebral fissures and joint contractures, findings not noted in other patients with WZS. Chemke et al. [1992] suggest that this child had Rolland-Desbuquois type of dyssegmental dysplasia. Therefore, our patients represent the first individuals known to have neural tube defect and WZS. However, not all children with the disorder have had neuroimaging studies to detect less obvious structural abnormalities of brain.

Twin B has persisting global developmental delay which is likely to relate to the effects of the encephalocele augmented by the occurrence of neonatal meningitis and hearing loss. Hearing loss has been identified in other children with WZS [Weissenbacher and Zweymüller, 1964; Cortina et al., 1977; Chemke et al., 1992], but, in this child, it is difficult to be certain whether it is part of the syndrome or a consequence of neonatal meningitis and its treatment. Apnea, a significant problem in infancy for twin B, was felt to be central in origin rather than obstructive as his micrognathia was mild. In other infants with WZS, respiratory distress and apnea have been thought to be consequent to the anatomic effects of the Robin sequence.

Growth rate is normal in our patients but no "catch up" has occurred; rhizomelic proportions continue to be apparent at age 3 years. Most of the children with WZS have shown normalization of growth with resolution of

proximal limb shortness with variability in the age at which this occurred [Chemke et al., 1992].

We conclude that neural tube defect may be part of the spectrum of expression of WZS and, if confirmed as part of the phenotype by its presence in additional patients, would also serve to differentiate WZS from Stickler and Marshall syndromes.

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