Roberts/SC phocomelia syndrome (RBS) is a rare but distinct genetic disorder with an autosomal recessive inheritance pattern. It has been associated with microcephaly, craniofacial malformation, cavernous hemangioma, encephalocoele, and hydrocephalus. There are no previously reported cases of RBS with intracranial aneurysms. The authors report on a patient with a history of RBS who presented with a spontaneous posterior fossa hemorrhage. Multiple small intracranial aneurysms were noted on a preoperative CT angiogram. The patient underwent emergency craniotomy for evacuation of the hemorrhage. A postoperative angiogram confirmed the presence of multiple, distal small intracranial aneurysms. (DOI: 10.3171/2011.8.PEDS11117)

Key Words • Roberts syndrome • aneurysm • intracranial hemorrhage • congenital

Abbreviations used in this paper: AICA = anterior inferior cerebellar artery; MCA = middle cerebral artery; RBS = Roberts/SC phocomelia syndrome.

Roberts/SC phocomelia syndrome is a distinct autosomal recessive genetic syndrome that results from a mutation of the ESCO2 gene on 8p21. Among the more common clinical findings are mental retardation, tetraphocomelia, syndactyly or oligodactyly, arm and leg bone synostoses, microcephaly, prominent wide-spaced eyes, corneal clouding, hypoplastic nasal alae, cleft lip and palate, heart defects, kidney defects, cryptorchidism, enlarged phallus, facial hemangioma, and growth retardation. Frequently seen neurosurgical anomalies include microcephaly and hydrocephalus. Superficial hemangioma involving the face and scalp are commonly seen in patients with RBS. The syndrome has not been associated with intracranial aneurysms. We report on a patient with RBS who presented with a spontaneous posterior fossa hemorrhage and multiple, distal, small saccular intracranial aneurysms.

Case Report

History and Examination. This 10-year-old girl with a karyotype-proven diagnosis of RBS had several episodes of emesis at school and was noted to be mildly lethargic. Her level of consciousness deteriorated further during emergency transportation to the hospital. On her initial evaluation at the hospital, she was able to localize bilaterally and was assigned a Glasgow Coma Scale score of 8T.

Her medical history was significant for RBS. At her neurological baseline, she had a normal level of alertness and was able to communicate using 12 meaningful signs. She had no speech. She was mobile with the use of a walker, and she attended a special school that included occupational and physical therapy. She was fully dependent for all activities of daily living. Her clinical history included microcephaly, surgical repair of left coronal synostosis 8 years earlier, and hydrocephalus for which she had undergone ventriculoperitoneal shunting shortly after birth with no revisions. She had imaging findings consistent with a Chiari malformation Type I. In addition, she had many other features typical of RBS, including congenital absence of the radii, torticollis, corneal clouding, syndactyly, persistent ductus arteriosus, nephrocalcinosis, facial hemangioma, and bilateral clubfeet. The RBS diagnosis had been confirmed by karyotype, showing the characteristic finding of premature centromere division.

Noncontrast CT scanning of the head showed a posterior fossa hemorrhage involving the bilateral cerebellar parenchyma as well as the fourth ventricle, with slight ex-
tension into the third ventricle via the aqueduct of Sylvius (Fig. 1). The hemorrhage measured 3.5 cm transversely and 4 cm in the craniocaudal dimension. Computed tomography angiography showed multiple distal intracranial aneurysms. None of the most clearly defined aneurysms were adjacent to the area of hemorrhage. However, a small outpouching of the right AICA was identified at the anterior margin of the hematoma (Fig. 2).

Operation. Given the patient’s poor neurological status, within 1 hour of her arrival in the emergency department she was taken to the operating room for a suboccipital craniectomy and evacuation of the hematoma. The hematoma was completely evacuated (Fig. 3). An area of arterial bleeding was encountered at the anterior margin of the hematoma cavity and was subjected to bipolar coagulation. A conventional angiogram was obtained immediately postoperatively, confirming the presence of multiple, distal, small saccular intracranial aneurysms at the distal right posterior cerebral artery, the right MCA bifurcation, the distal right MCA, the distal left MCA, and the distal anterior cerebral artery (Figs. 4 and 5). No aneurysms were identified adjacent to the hematoma cavity.

Postoperative Course. The patient remained in the intensive care unit for 14 days, followed by a 26-day stay in an inpatient rehabilitation unit. No coagulopathy or platelet abnormalities were detected. Blood cultures were negative for bacterial growth. An echocardiogram showed no evidence of cardiac dysfunction, vegetation, or thrombus. She had no physical signs of collagen vascular disease. She showed progress toward her previous functional level during her inpatient stay. At the time of hospital discharge, she was able to use sign language to communicate and could ambulate with a walker.

Brain imaging with MR angiography was performed 6

Fig. 1. Axial noncontrast head CT obtained at the time of patient presentation, showing a large intraparenchymal hemorrhage within the posterior fossa.

Fig. 2. Sagittal CT angiogram showing a small outpouching of the AICA at the anterior margin of the intraparenchymal hematoma (arrow).

Fig. 3. Axial T2-weighted MR image obtained following hematoma evacuation, showing no flow voids in the region of the hemorrhage.
months postoperatively, showing complete resolution of the hemorrhage and no change in intracranial vasculature. By 9 months postoperatively, the patient had returned to her preoperative functional status. She was able to ambulate with the use of a walker and to participate in occupational and physical therapy at her baseline level of function. Although she was left-handed prior to the hemorrhage, she now favors her right hand. No further surgical treatment has been recommended, although we intend to monitor these aneurysms with CT angiography in 1 year to evaluate for change or growth of the intracranial aneurysms.

Discussion

In 1919, Roberts11 described bilateral cleft lip and palate, intermaxillary protrusion, and hypoplasia of the arms and legs in 3 children born of a consanguineous Italian couple. Four cases with similar clinical findings were presented12 before Appelt1 recognized the constellation of malformations now known as “Roberts syndrome” in 1966. Early definitions of this syndrome included cleft lip and palate, tetraphocomelia with oligodactyly, exophthalmos, ocular hypertelorism, microcephaly, ocular and orific abnormalities, and clitoral or penile enlargement.1 In 1969, after observing 2 families with surnames beginning with “S” and “C,” Herrman et al.5 described SC phocomelia syndrome, a clinical syndrome involving symmetric reductive malformations of the limbs, flexion contractures of joints, capillary hemangiomas of the head, cloudy corneas, hypoplastic cartilages, growth retardation, and autosomal recessive inheritance. Patients with SC phocomelia displayed milder physical defects and mental retardation in comparison with the patients with RBS, although it had long been suspected that the disorders were phenotypic variants of the same disease.

In 1987, Römke et al.12 reported the diagnosis of either RBS or SC phocomelia individually among 5 siblings. Follow-up on Herrman and colleagues’13 “C” patient, published in 1992, included chromosome studies showing evidence of premature centromere separation.2 Similar chromosomal abnormalities in cells in metaphase were observed when studying patients with RBS as well as those with SC phocomelia.1,4-6,13,16,17 Cell hybrid and chromosome transfer complementation studies implicated mutations in the same gene.18 Genetic mapping was accomplished by Vega et al.19 who studied 7 Colombian families affected with RBS and discovered a common ancestor in 4 of the families. A region of homozygosity on 8p21 containing the ESCO2 gene was identified as the disease-associated locus in all patients. ESCO2 encodes ESCO2, a protein product belonging to the Eco1/Ctf7 family of acetyltransferases that are known to regulate sister chromatid cohesion during the S phase.19

Roberts syndrome displays autosomal recessive inheritance. Both homozygous and compound heterozygous mutations have been found to result in the RBS phenotype, and all involve the ESCO2 gene.17,19 The RBS phenotype varies widely in severity and is produced by cohesion defects, reduction of proliferation, and mitomycin C sensitivity,17 although the severity cannot be predicted by genotype.11 The RBS cellular phenotype is characterized by premature centromere separation, lagging chromosomes, aneuploidy, micronuclei, and decreased cell proliferation.19 The diagnosis of RBS is confirmed by the finding of heterochromic repulsion on cytogenetic testing. The characteristic “tram-track” appearance of the sister chromatids is due to the absence of constriction at the centromere, causing premature centromere separation and sporadic aneuploidy seen in neonatal fibroblasts and lymphocytes, or fetal chorionic villi and amniocytes.16

Clinical features associated with RBS include mental retardation, tetraphocomelia, syndactyly or oligodactyly, arm and leg bone synostoses, microcephaly, prominent wide-spaced eyes, corneal clouding, hypoplastic nasal alae, cleft lip and palate, heart defects, kidney defects, cryptorchidism, enlarged phallus, facial hemangioma, and growth retardation.17 The syndrome can cause stillbirth and spontaneous abortion, while a small number of individuals survive into adulthood. Roberts syndrome has also been known as pseudothalidomide syndrome, Appelt-Gerken-Lenz syndrome, hypomelia-hypotrichosis-facial hemangioma syndrome, and tetraphocomelia-cleft palate syndrome.4

The patient in the featured case presented with spontaneous intracranial hemorrhage. During surgical evacuation, arterial bleeding was encountered at the anterior margin of the hematoma. The CT angiogram obtained prior to surgery demonstrated a small outpouching within the right AICA at the anterior margin of the hema-

Fig. 4. Anteroposterior (left) and lateral (right) left vertebral artery angiograms showing distal saccular right posterior cerebral artery aneurysms (large arrows). Multiple areas of arterial narrowing and dilation are identified within the posterior fossa in the resection cavity (small arrows).

Fig. 5. Anteroposterior (left) and lateral (right) left internal carotid artery angiograms showing saccular aneurysms (arrows) involving the distal left MCA, left pericallosal artery, distal left anterior cerebral artery, right MCA bifurcation, and distal right MCA.
Multiple intracranial aneurysms in Roberts syndrome

toma in the area of arterial bleeding seen during surgery. These findings suggest that the hemorrhage may have been caused by a small ruptured aneurysm. Follow-up angiography demonstrated multiple, distal, small saccular intracranial aneurysms. To our knowledge, RBS has not been previously associated with intracranial aneurysms. Superficial hemangiomata involving the face and scalp are commonly seen in patients with RBS; however, there are only a few prior cases of RBS associated with intracranial vascular disease. Two patients with RBS have also had intracranial cavernous malformations,

10, 14 both lesions arising in the oculomotor nerve. Herrmann and colleagues’ “C” patient demonstrated moyamoya disease. 2 Although altered or incomplete development occurs in several organs of different cell origins in RBS, ESCO2 protein function has not yet been implicated in neurovascular formation. ESCO2 expression has been shown to peak during the S phase, 18 which suggests that the protein has a specific function in establishing sister chromatid cohesion during the S phase. ESCO2 deficiency leads to cohesion defects and sensitizes cells to certain mechanisms of DNA damage. 18 This deficit in the maintenance of genomic stability during cell division very likely explains the various developmental defects that typify RBS, including abnormalities in neurovascular integrity.

Patients with RBS present with variable severity of the syndrome, and the life expectancy of children with RBS depends on the severity of symptoms. Although mildly affected individuals can survive into adulthood, our patient was affected more severely. In general, treatment in such infected individuals can survive into adulthood, our patient

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