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Case Report

Roberts Syndrome Presenting with Aneurysmal Intraparenchymal Hemorrhage

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Abstract

Introduction: Roberts syndrome is a rare genetic disorder characterized by intrauterine and postnatal growth retardation, limb and craniofacial abnormalities, intellectual disability, associated with diseases such as heart disease and polycystic kidneys. In the international and national literature, there is little evidence related to the presentation of Roberts syndrome and vascular malformations such as intracranial aneurysms. Intraparenchymal hemorrhage of aneurysmal origin is a rare clinical entity. Presentation in paediatric age is unusual; where intracranial aneurysms represent less than 5% of all cases and only about 5% of intraparenchymal hemorrhages have an underlying aneurysm.

Case Presentation: We present the case of a 17-year-old patient diagnosed with Roberts syndrome and imaging studies showing multiple intracranial aneurysms; whose clinical debut was due to an intraparenchymal hemorrhage.

Objective: To describe the clinical presentation and management of intracranial aneurysms in a paediatric patient with Roberts Syndrome.

Conclusions: The association of Roberts syndrome with intracranial aneurysms is rare; the present case being relevant due to the unusual nature of its clinical presentation and the challenge imposed by its neurosurgical management.

Keywords: Roberts Syndrome; Intracranial Aneurysm; Intraparenchymal Hemorrhage

Introduction

Intraparenchymal hemorrhage is a collection of blood within the brain parenchyma secondary to non-traumatic vascular rupture, presenting with high morbidity and mortality. It can be classified as primary or secondary; the latter accounts for 20% and its origins are diverse, including congenitally abnormal or neoformed vessels, vasculitis, coagulation disorders, and in 9% of cases, the cause cannot be determined [1].

Aneurysmal intraparenchymal hemorrhage is a rare clinical entity. Pediatric presentation is unusual, as intracranial aneurysms represent less than 5% of all cases, and only about 5% of pediatric intraparenchymal hemorrhages have an underlying aneurysm [2]. An intracranial aneurysm is defined as a permanent and localized dilation of a segment of an artery in the cerebral circulation, generally secondary to structural weakness of the vessel wall and of variable etiology, whether degenerative, congenital, or traumatic. These have a prevalence of 0.1% to 9%, occurring more frequently in adults than in children [1,3].

In the process of cerebral vessel angiogenesis, massive failure in cell proliferation, migration, and apoptosis due to genomic instability abruptly interrupts the remodeling process, preventing the formation of a normal vascular network and favoring the persistence of vascular connections that give rise to direct and complex vascular malformations [4,5].

Roberts syndrome (RS), also known as pseudothalidomide or phocomelia syndrome, is a genetic disease with autosomal recessive inheritance, whose characteristic clinical picture includes intrauterine and postnatal growth retardation, severe shortening of the limbs with radial defects, and craniofacial anomalies [6].

The first reference was made at the beginning of the 20th century, specifically in 1919, by Roberts, in three siblings with extremity malformations. Then, in 1969, Herrmann described it as pseudothalidomide syndrome or SC phocomelia syndrome, due to the presence of reductive limb defects similar to those observed in thalidomide embryopathy [6].

The genetic alteration is caused by a mutation in the ESCO2 gene, which encodes a protein belonging to the Eco1/Ctf7 acetyltransferase family involved in establishing sister chromatid cohesion during the S phase. This leads to delayed cell division, increased apoptosis, and impaired cell proliferation [6,7].

Regarding its epidemiology, it has been described that it affects individuals of both sexes equally, and although it is very rare, it has been found in all geographical areas, with approximately 150 cases of various ethnicities reported in the literature. It has a high mortality rate, though mildly affected patients can survive to adulthood [7].

In the scientific community, there is little information regarding Roberts syndrome, generally focused on its etiology and the various anomalies related to the osteomyoarticular system. Despite the well-documented studies on its genesis and the changes in cell proliferation and apoptosis, there are no reports to date on its association with vascular malformations such as cerebral aneurysms. Therefore, the present article aims to describe the clinical presentation of a patient with Roberts syndrome and multiple intracranial aneurysms, whose initial manifestation was an intraparenchymal hemorrhage

Case Report

Patient history

A17-year-old male patient with a past medical history of Roberts syndrome. Since birth, he has received multidisciplinary follow-up due to multiple congenital malformations affecting nearly all organ systems. His surgical history includes several orthopedic interventions performed at the William Soler and Frank País García Hospitals for the correction of extremity deformities. In terms of neurosurgical history, he suffered a subarachnoid hemorrhage in 2021, which required surgical management at the Juan Manuel Márquez Pediatric Hospital. In 2024, he presented with an acute onset of altered consciousness. No relevant toxic habits or psychosocial risk factors are recorded.

Physical examination

Multiple congenital malformations were observed in the extremities, including short arms, fixed flexion contracture of both elbows, phocomelia with bilateral absence of the forearms, congenital hypoplasia of both thumbs, short thighs, flexion contracture of both knees, bilateral fibular agenesis, bilateral valgus ankles, and bilateral clubfeet (Figure 1). On neurological examination, anisocoria of the left eye and a deteriorated level of consciousness were noted.

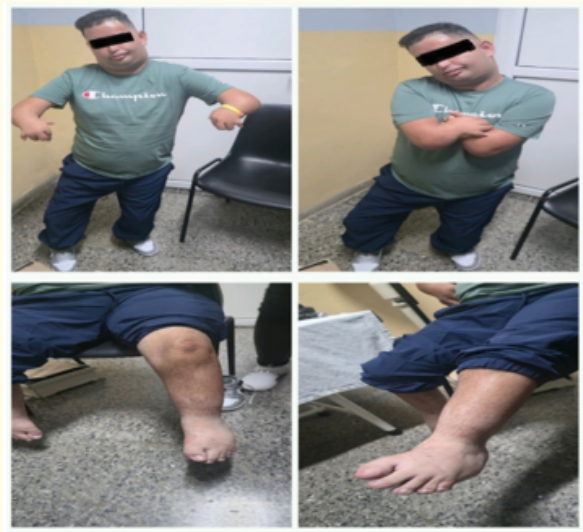

Figure 1: Current photos of the patient.

Imaging findings

- **Brain MRI (January 15, 2024):** Revealed bifrontal encephalomalacia with left predominance, non-communicating hydrocephalus with marked dilation of the lateral, third, and fourth ventricles, and signs of interstitial edema. Deformity of the pons was observed, along with a small focal hyperintense area of vascular appearance. On T1-weighted sequences, a hyperintense left frontal lesion measuring 1.2 x 1.6 cm was identified, consistent with methemoglobin and suggestive of a prior hemorrhagic sequela. A wide left frontal craniectomy defect was also noted. Angiographic sequences showed elongation of the cerebral vessels, with an extended pericallosal artery secondary to hydrocephalus, and a rounded hyperintense image projecting into the marginal callosal artery, measuring 3 mm in diameter, compatible with an aneurysmal formation at that level (Figure 2).
- **Cerebral panangiography of both carotid and vertebral arteries (April 2, 2024):** Demonstrated the presence of multiple cerebral aneurysms located in the left and right Sylvian projections (measuring 2 mm and 4mm,respectively), at the junction of the pericallosal and marginal callosal arteries (2.5 mm), and in the posterior cerebral artery (2 mm). The largest aneurysm, located in the left Sylvian projection, had a pyriform appearance and dimensions of 7 x 14 mm. All cerebral vessels appeared arched and elongated, and the right vertebral artery was observed to be smaller in caliber (Figure 3). Electrophysiology
- **Electroencephalogram (June 9, 2025):** A 19-channel EEG performed during spontaneous sleep showed entry into the initial stages of non-REM sleep, with few wakefulness windows. It revealed paroxysmal, intercritical, inactive activity of slight intensity, manifested as angular slow waves in the left frontotemporal region. These findings were compatible with possible mild dysfunction of the cortical gray matter, to be correlated with the patient's clinical presentation.

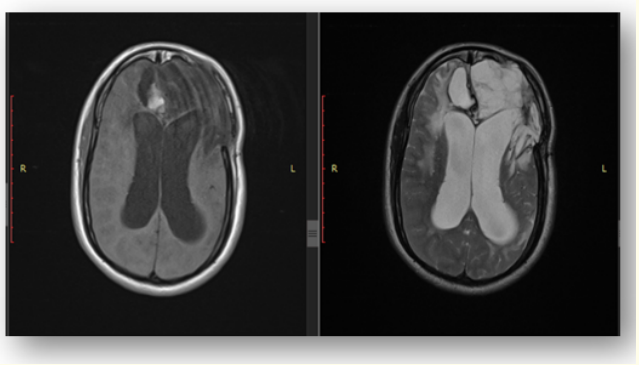

Figure 2: Magnetic Resonance Imaging Study.

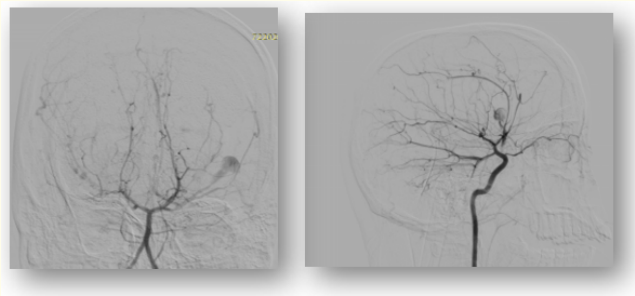

Figure 3: Cerebral Panangiography Study.

Surgical management and outcome

Following the diagnosis of intraparenchymal hemorrhage, surgical treatment was decided upon after a collective discussion within the Neurosurgery Department of the Juan Manuel Márquez Pediatric Hospital. The procedure consisted of a decompressive craniectomy and aspiration of the left frontal hematoma. The postoperative course was favorable, with no complications related to the surgical bed.

Follow-up and conservative management

Subsequent cerebral panangiography confirmed the presence of multiple aneurysms. However, due to their location, size, and the patient's underlying comorbidities, surgical intervention was deemed unfeasible. Therefore, medical treatment and expectant management were prioritized as the definitive therapeutic strategy.

Discussion

Roberts syndrome (RS) is a rare autosomal recessive disorder characterized by pre- and postnatal growth retardation. Its prevalence is undetermined, estimated at less than 1 in 300,000 births. According to Orphanet statistics, approximately 150 cases have been described in the world literature, with around 80 cases

confirmed molecularly. This rarity makes it difficult to establish a precise incidence, and many cases may go undiagnosed, especially in regions with limited resources. In Cuba, there is little data regarding its national incidence [8,9].

The phenotype of RS is highly variable, presenting as a spectrum ranging from severe to milder forms. Clinical manifestations include extremity malformations such as severe limb shortening (phocomelia), oligodactyly with aplasia or hypoplasia of the thumb, syndactyly, and clinodactyly. Defects also involve large genitals, congenital heart disease, cystic kidneys, and intellectual disability [10].

Numerous craniofacial alterations may be present; the most frequent are facial: cleft lip and palate, premaxillary protrusion, micrognathia, malar hypoplasia, hypertelorism, exophthalmos, corneal opacities and cataracts, aquiline nose, low-set ears, facial hemangiomas, and hypoplasia of the ala nasi [10]. Among the cranial anomalies are microcephaly, microbrachycephaly, and frontal encephalocele with complete median facial cleft [9]. However, there is very little documented association in the scientific literature with arteriovenous malformations, and even less so with cerebral aneurysms.

Gene Reviews and Orphanet, in their study on ESCO2 spectrum disorder, briefly reference acquired neurological complications in patients with RS, emphasizing the risk of cerebrovascular disease, including aneurysms and vascular malformations, which warrants neurological follow-up in patients who survive into adolescence [8]. However, no detailed case reports are provided in this regard.

Cerebral aneurysms have a variable global distribution, with an estimated prevalence in the general population ranging between 3% and 5% according to population studies, and a higher incidence in adults than in infants. This estimate is based on autopsy findings and imaging studies revealing that most aneurysms remain asymptomatic throughout life [11]. Specific investigations have documented that approximately 1 in 50 people carries an unruptured cerebral aneurysm, although only a minimal fraction of these will manifest clinically. A retrospective study conducted in Quito, Ecuador, by Martínez-Burbano., *et al*. (2023) analyzed 8,390 patients treated in neurology over a 9-year period, identifying 450 cases diagnosed with cerebral aneurysm, representing a prevalence of 5.3% in their series, slightly higher than the reported global averages [12].

In the present case, the diagnosis of multiple aneurysms was made following a neurological presentation consistent with intraparenchymal hemorrhage and confirmation by neuroimaging studies.

The distribution of cerebral aneurysms shows an age-related pattern, being more frequent in people between 30 and 60 years of age. The study by Martínez-Burbano., *et al*. identified the highest frequency in the 50 to 59year age group. Regarding sex, there is a clear predominance in women, who have greater susceptibility to developing this pathology compared to men. In the pediatric population, cerebral aneurysms represent less than 4% of all such conditions [12].

Risk factors associated with the development and rupture of cerebral aneurysms are diverse and include both genetic and environmental elements. Hemodynamic factors such as arterial hypertension weaken the arterial wall due to mechanical stress with consequent vascular inflammation, and are among the main modifiable factors. Other risk factors include toxins such as smoking, alcoholism, and consumption of substances such as cocaine and amphetamines. Afamily history of aneurysms in firstdegree relatives substantially increases the risk [12,13]. In the case under study, no environmental risk factors are evident, leaving the genetic factor in the first place, closely related to the genomic alterations of RS and the disruption of cell proliferation and apoptosis, which could be involved in the predisposition of cerebral vessels to dilation.

According to the study Intracranial Aneurysms: Pathology, Genetics, and Molecular Mechanisms, aneurysm formation shows pathological alterations in cerebral vessels, including disintegration of the internal elastic laminae, irregular luminal surface, myointimal hyperplasia, infiltration of inflammatory cells, disorganization of the tunica media, and hypocellularity. These alterations, in an anomalous vessel, increase the risk of aneurysm formation, for example when congenital syndromes coexist [14].

Several congenital syndromes linked to intracranial aneurysms are reported in the literature, including autosomal dominant polycystic kidney disease, EhlersDanlos syndrome type IV, microcephalic osteodysplastic primordial dwarfism type II, LoeysDietz syndrome, Marfan syndrome, and neurofibromatosis type 1. Their pathogenesis varies, from connective tissue disorders

such as EhlersDanlos syndrome (which affects type III collagen fiber production, with implications for the arterial wall) to polycystic kidney disease (which presents a high incidence together with aneurysms) [13,14].

Acommonelement amongthese syndromes is the alterations they produce in structures embryologically derived from the mesodermal layer, that is, connective tissue (bones, cartilage, tendons), muscle, the cardiovascular system, and with primary involvement of most of the axial and appendicular musculoskeletal system [15]. Roberts syndrome is considered a condition that significantly involves mesodermderived structures such as the extremities, face, kidneys, and heart. The ESCO2 gene mutation causes a defect in the active cohesion of cell checkpoints, triggering apoptosis. This generalized cell loss during critical periods of embryonic development, particularly in tissues undergoing rapid proliferation such as the mesoderm, constitutes one way to explain the clinical manifestations [8].

The authors consider that, when analyzing this context and the relationship that exists between congenital syndromes linked to aneurysm development, this could represent a pathogenic pathway in the case under study, where multiple aneurysms and RS occur simultaneously. International references on this association are very scarce; to date, evidence is found in two notable articles with similar presentations. One of them, Spontaneous intracranial hemorrhage and multiple intracranial aneurysms in a patient with Roberts/SC phocomelia syndrome [16] (2011), was the first case report to document this presentation with a spontaneous intraparenchymal hemorrhage of the posterior fossa. The second, Intracranial aneurysms in SC phocomelia syndrome– a rare but important association [17] (2020), reflects the same presentation. However, both articles are limited to case reporting and do not address the pathophysiology or possible association between these two entities.

Cerebral aneurysms present characteristic localization patterns that influence clinical behavior and therapeutic options. Approximately 85% develop in the anterior portion of the circle of Willis, while the remaining 15% are located in the vertebrobasilar system (posterior circulation). The most frequent locations include: the anterior communicating artery complex (3539%), the origin of the posterior communicating artery from the internal carotid artery (3539%), the bifurcation of the middle cerebral artery (20%, frequently associated with multiple aneurysms), and the basilar and other posterior circulation arteries (5%, generally associated with greater therapeutic complexity) [16].

Aneurysms are classified into three main morphological types: saccular (6698%), the most prevalent form, characterized by cherryshaped bulges originating predominantly at arterial bifurcations with a defined neck, body, and dome; fusiform, which represent elongated, dilated, and tortuous arterial segments affecting the artery circumferentially, lacking a defined neck and usually located more frequently in the posterior circulation; and dissecting aneurysms, which consist of intramural hematomas creating a false lumen within the injured arterial wall [1,12].

Stratification by size has significant prognostic and therapeutic implications, classifying them as: very small (less than 3 mm), small (less than 11 mm, the most frequent), large (1125 mm), and giant (greater than 25 mm) [1,12,13]. Pediatric aneurysms show a distinctive localization pattern, with more frequent involvement of peripheral arteries compared to the predominance of the circle of Willis in adults. Morphologically, giant aneurysms are more frequent in the pediatric population, and there is a greater proportion of nonsaccular forms (fusiform and dissecting) compared to adults [14]. Relevant to this case is the presence of aneurysms in both the anterior and posterior circulation, mostly saccular (the most frequent morphology) and small in size.

The clinical manifestations of cerebral aneurysms vary considerably depending on their state and size. Unruptured aneurysms are frequently asymptomatic and discovered incidentally. When symptomatic, they are usually due to compression of adjacent structures: ocular paralysis (compressions of cranial nerves III, IV, V, or VI), diplopia, strabismus, orbital pain, visual deficits due to chiasmatic compression, and headache [1,8,15]. Ruptured aneurysms typically manifest with sudden and intense headache, frequently described as “the worst headache of my life” or “thunderclap headache,” which may be accompanied by nausea, vomiting, photosensitivity, altered consciousness, and seizures. It is crucial to recognize the sentinel headache, which may occur days or weeks before a complete rupture due to minor warning bleeding [1,13].

Complications of ruptured cerebral aneurysms are potentially devastating: subarachnoid hemorrhage (SAH) is the most frequent immediate complication; cerebral vasospasm occurs in up to 30%of cases; hydrocephalus; intraparenchymal hemorrhage associated with focal neurological deficits; and death—approximately 10% of patients die before receiving medical attention, and an additional 50% die within the first month without treatment. In the pediatric population, the mortality rate from aneurysm rupture is 1023% [17].

Globally, intraparenchymal hemorrhage represents approximately 20% to 28% of all cerebrovascular diseases. Age is a primary risk factor in adults; however, in pediatric ages, its incidence is much lower, although it accounts for a greater proportion of childhood strokes, especially in the first years of life [2,4]. When analyzing the relationship with aneurysms, it is crucial to highlight that although aneurysm rupture is a classic cause of intraparenchymal hemorrhage, it is a less frequent cause of isolated IPH. According to the study Global, regional, and national burden of intracerebral hemorrhage, 19902021, it is estimated that between 5% and 15% of spontaneous IPHs have an aneurysm as the underlying etiology. Despite SAH being the most frequent presentation of ruptured aneurysms of nontraumatic origin in both adults and children, in the present case, the presentation was through an intraparenchymal hemorrhage related to deep aneurysmal locations and arterial hypertension.

The management of these vascular pathologies is individualized according to the characteristics of the aneurysm, the patient's condition, and available resources, ranging from monitoring with serial neuroimaging (the preferred strategy for small asymptomatic aneurysms in the anterior circulation, given their low rupture risk) to endovascular treatment (including embolization and placement of remodeling stents, less invasive than open surgery) and open surgical clipping (which involves craniotomy and clip placement on the aneurysm neck, remaining the gold standard for complex aneurysms) [17,18]. Aggressive medical management includes strict blood pressure control, prevention of vasospasm with calcium channel blockers, eradication of modifiable risk factors, and management of complications [18].

However, in the present case, surgical management of the multiple aneurysms was not feasible due to the multiple comorbidities linked to Roberts syndrome, the deep locations of the aneurysms, and the high risk of postoperative complications associated with anesthesia given the patient's malformations. Current evidence suggests that, although diagnostic and therapeutic techniques for cerebral aneurysms have evolved, optimal management requires an individualized assessment that considers location, size, and underlying pathologies.

The association between Roberts syndrome and multiple intracranial aneurysms—particularly presenting with intraparenchymal hemorrhage—is scarcely documented, and no studies to date have specifically addressed the management of these aneurysms in this population, highlighting the need for further research and longterm neurological surveillance in RS patients.

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