FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Genetic cerebral arteriopathies in children: a review

REVISÃO NARRATIVA

ÁREA CIENTÍFICA DE PEDIATRIA

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ABRIL/2021

Faculty of Medicine

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Genetic cerebral arteriopathies in children: a review

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1. LIST OF ABREVIATIONS

ACA	Anterior cerebral artery
AIS	Arterial ischemic stroke
APW	Aortopulmonary window
CA	Cerebral angiography
CBF	Cerebral blood flow
CNS	Central nervous system
CNV	Copy number variation
CO_2	Carbon dioxide
CT	Computed tomography
DMN	Distal Motor Neuropathy
DS	Down syndrome
ECA	External carotid artery
FLAIR	Fluid-attenuated inversion recovery
ICA	Internal carotid artery
IV	Intravenous
LUMBAR	Lower body hemangiomas (L); urogenital anomalies (U); myelopathy (M); bone deformities (B); anorectal malformations/arterial anomalies (A); renal anomalies (R)
MCA	Middle cerebral artery
MD	Menkes disease
MMD	Moyamoya disease
MMS	Moyamoya syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MSMDS	Multisystemic Smooth Muscle Dysfunction Syndrome
NF-1	Neurofibromatosis type 1
OHS	Occipital Horn Syndrome
PCA	Posterior cerebral artery

PDA	Persistent ductus arteriosus
PET	Positron Emission Tomography
PHACE	Posterior fossa malformations (P), hemangiomas (H), arterial anomalies (A), coarctation of the aorta and cardiac defects (C), and eye abnormalities (E)
PHACES	Posterior fossa malformations (P), hemangiomas (H), arterial anomalies (A), coarctation of the aorta and cardiac defects (C), eye abnormalities (E), and sternal clefting and/or supraumbilical abdominal raphe (S)
PWI	Perfusion-weighted imaging
RBCs	Red blood cells
RNF213	Ring finger protein 213
SCD	Sickle cell disease
SMC	Smooth-muscle cell
SPECT	Single Photon Emission Computed Tomography
TCD	Transcranial doppler
TIA	Transient ischemic attack
UCH	Unilateral cerebellar hypoplasia
USA	United States of America
VIPS	Vascular effects of Infection in Pediatric Stroke
YY1AP1	Yin yang 1-associated protein 1

2. ABSTRACT

A focal and structural anomaly of the arterial wall is usually called arteriopathy. Arteriopathies can have multiple etiologies, from genetic to traumatic, infectious, or inflammatory. The issue about these diseases is that their main presentation is childhood arterial ischemic stroke (AIS). As genetic arteriopathies are rare conditions, it is important to summarize the known and relevant clinical information.

Moyamoya is an angiographic pattern characterized by steno-occlusion in the arteries of the brain arterial circle (circle of Willis) associated with the development of compensatory circulation showing as a “puff of smoke”. It can be idiopathic and be called Moyamoya disease or it can be associated with other conditions, such as sickle cell disease, neurofibromatosis type 1 or trisomy 21, and be denominated Moyamoya syndrome. Treatment is usually with revascularization procedures.

ACTA2 mutations, particularly in arginine at position 179, cause Multisystemic Smooth Muscle Dysfunction Syndrome. The cerebrovascular disease phenotype includes a combination of ectasia and stenosis and abnormally straight course, particularly in the arteries of the Circle of Willis. As it is a syndrome affecting multiple systems, it demands a multidisciplinary approach, with various surgery procedures to correct the anomalies these patients present. Symptomatic measures and revascularization procedures can also be used.

Grange Syndrome is characterized by severe early-onset vascular disease, whom etiology is mutations of *YY1AP1* gene. It presents with hypertension and multifocal steno-occlusive lesions of renal, cerebral, and abdominal arteries, associated with other multisystemic features. Its cerebrovascular pattern is similar to Moyamoya.

Menkes disease (MD) is a rare X-linked recessive condition caused by mutations in *ATP7A* gene. There are various phenotypes associated with these mutations with different degrees of severity. Increased artery tortuosity is the typical diagnostic feature of MD. As this is a condition characterized by copper deficiency, diminished levels of serum copper and ceruloplasmin suggest the diagnosis. Further testing can be used to complement the laboratory study. Copper parenteral or subcutaneous administration may be a successful treatment.

PHACE acronym stands for posterior fossa malformations (P), hemangiomas (H), arterial anomalies (A), coarctation of the aorta and cardiac defects (C), and eye abnormalities (E). A simple genetic etiology for this syndrome has yet not been identified. Specialists from different surgical areas may be necessary to treat the comorbidities.

The cerebrovascular disease in all these conditions is generally diagnosed with magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and, when possible, with conventional angiography. Moreover, as they are genetically caused, genetic testing plays an important role in their diagnosis.

Keywords: Genetic arteriopathies; Stroke; Children

3. RESUMO

Anomalias focais e estruturais da parede arterial são denominadas arteriopatias e podem ter múltiplas etiologias, desde genéticas a traumáticas, infeciosas ou inflamatórias. Um dos aspetos problemáticos relacionado com estas patologias é que a sua apresentação principal é com acidente vascular cerebral (AVC) isquémico na infância. Como as arteriopatias genéticas são condições raras, é importante resumir os dados conhecidos e relevantes.

Moyamoya é um padrão angiográfico caracterizado por esteno-oclusão das artérias do polígono arterial do cérebro (polígono de Willis), associado ao desenvolvimento de circulação compensatória demonstrada como um “sopro de fumo”. Pode ser idiopático e ser denominado de doença de Moyamoya, ou pode estar associado a outras condições, como a anemia de células falciformes, neurofibromatose tipo 1 ou trissomia 21, designando-se por síndrome de Moyamoya. O tratamento é normalmente com procedimentos de revascularização cirúrgica.

As mutações do gene *ACTA2*, particularmente na arginina na posição 179, causam a Síndrome Multissistémica de Disfunção do Músculo Liso. O fenótipo da doença cerebrovascular inclui a combinação de ectasia e estenose e um curso anormalmente reto particularmente nas artérias do polígono. Como esta síndrome afeta múltiplos sistemas, é necessária uma abordagem multidisciplinar com vários procedimentos cirúrgicos para corrigir as anomalias que estes pacientes apresentam. Medidas sintomáticas e procedimentos de revascularização também podem ser usados.

A Síndrome de Grange é caracterizada por doença vascular severa de início precoce, cuja etiologia é atribuível a mutações no gene *YY1AP1*. Apresenta-se com hipertensão e lesões esteno-oclusivas multifocais das artérias renais, cerebrais e abdominais, associadas a outras manifestações multissistémicas. O padrão cerebrovascular é semelhante ao Moyamoya.

A Doença de Menkes (MD) é uma condição rara, de hereditariedade recessiva ligada ao X, causada por mutações no gene *ATP7A*. Há vários fenótipos associados a estas mutações com diferentes graus de gravidade. Tortuosidade arterial é a manifestação típica e diagnóstica da MD. Como esta é uma condição associada à deficiência de cobre, níveis diminuídos de cobre sérico e ceruloplasmina sugerem o diagnóstico. Investigação adicional pode ser usada para complementar o estudo laboratorial. A administração parenteral ou subcutânea de cobre pode ser um tratamento eficaz.

O acrónimo PHACE significa malformações da fossa posterior (P), hemangiomas (H), anomalias arteriais (A), coartação da aorta e defeitos cardíacos (C) e anomalias oculares (E). Ainda não foi identificada uma etiologia genética para esta síndrome. Especialistas de diferentes áreas cirúrgicas podem ser necessários para tratar as comorbilidades.

A afeção cerebrovascular de todas estas condições é, geralmente, diagnosticada por ressonância magnética (MRI), por angiografia por ressonância magnética (MRA) e, quando possível, por angiografia convencional. Adicionalmente, como são de etiologia genética, os testes genéticos têm um papel importante no diagnóstico.

Palavras-chave: Arteriopatias genéticas; Acidente vascular cerebral; Crianças

4. INTRODUCTION

A focal and structural anomaly of the arterial wall is usually called arteriopathy.[1] The VIPS – Vascular effects of Infection in Pediatric Stroke – study was a large prospective and international study conducted between 2009 and 2014 and it actually defines arteriopathy as "the imaging appearance of an *in situ* arterial abnormality (stenosis, irregularity, occlusion, banding, pseudoaneurysm, dissection flap) not attributable to an exogenous thrombus (e.g., cardioembolism) and not considered a normal developmental variant".[2] This arterial injury may result from various factors, such as infections, trauma and genetic causes.[3,4] A congenital arteriopathy may be due to abnormal arterial development. On the other side, an acquired arteriopathy may be caused by disruptions of normal homeostasis.[4]

Cerebral arteriopathies can be classified by etiology in genetic, traumatic, infectious, or inflammatory. They can also be classified by pattern of vessel involvement as focal or multifocal, involving large or small vessels, and the anterior or posterior circulation.[5] Another possible classification is only based on the dichotomy of inflammatory or noninflammatory.[3,5]

The common presentation of arteriopathies is an acute arterial ischemic stroke (AIS).[1,2,6] An AIS is defined by a combination of "a neurologic deficit of acute onset or, in neonates, seizures alone or other signs of neonatal encephalopathy, and radiologic images showing parenchymal infarcts conforming to known arterial territory(ies) and corresponding to clinical manifestations".[3] The presentation of a stroke in pediatric age can be non-specific,[7] but most children and adolescents will have an acute focal neurological syndrome. Headache and seizures are also common presentations.[8]

The prevalence of arteriopathy in the pediatric cases of AIS is estimated between 18% and 64%. Arteriopathies are important risk factors for primary stroke and also the strongest predictor of recurrence of these events, which makes their diagnosis critical.[5,9] Inflammation may also have influence in the recurrent AIS in cerebral arteriopathy.[4] Acute ischemic events often lead to poor outcomes that include death, neurological sequels and epileptic seizures[10], leading to a great impact in economic, social, personal and familiar levels.[11]

The VIPS study aimed to simplify diagnosis and classification of childhood arteriopathies, as this is a heterogenous and rare group of diseases, hard to be diagnosed by nonexperts.[2] The relevance of an uniform system to classify arteriopathies had already been recognized, but with the caveat that it would only be possible once genetic and

environmental factors acting together or apart in the pathogenesis of AIS could be fully understood.[3]

Stroke is a devastating event for a child and can be overwhelming not only to children and their families, but also at a socioeconomic level,[12] which makes it such an important topic to develop further research. Also, as genetic arteriopathies underlying stroke are such rare conditions, it is important to reflect about them and gather all the information known until now. Therefore, the purpose of this project is to present a narrative review on genetic arteriopathies in children and adolescents, focusing on the most relevant five: Moyamoya syndrome and disease, *ACTA2* variants-associated disease, Grange syndrome, Menkes disease and PHACE syndrome.

5. METHODS

In order to achieve the purpose of this study, literature search was collected from the electronic databases PubMed, Web of Science and Science Direct. The search was performed using a combination of the following terms: genetic arteriopathies in children, pediatric cerebral arteriopathies, classification and diagnosis of arteriopathy, Moyamoya syndrome, Moyamoya disease, Grange syndrome, *ACTA2* mutations, Menkes disease, PHACE syndrome.

A critic review of the literature thus collected was performed, including original articles, case reports and international reviews. Some of the studies quoted by the articles of the primary research were also analyzed and included in the revision. Particular relevance was given to articles published in the last 10 years; however, previous articles were quoted whenever considered useful. Articles not written in English were excluded from this analysis. Also, some articles were excluded by the title, the abstract or after their full analysis, if they did not address the aspects we have included in the review. Research was conducted between June 2020 and February 2021.

6. GENETIC ARTERIOPATHIES

6.1. Moyamoya Cerebral Arteriopathy

6.1.1. Definitions and Classification

Moyamoya is a cerebral arteriopathy characterized by progressive steno-occlusion of large vessels, mainly affecting the intracranial internal carotid artery (ICA) and/or the proximal middle cerebral arteries (MCA) and proximal anterior cerebral arteries (ACA) of the circle of Willis. It leads to diminished blood flow with development of a compensatory network of vessels at the base of the brain, equivalent to an image of a “puff of smoke” (Moyamoya in Japanese) in conventional angiography.[5,13,14] In some cases, this arteriopathy also involves the posterior circulation, including the basilar and posterior cerebral arteries, although this is a rare occurrence.[15]

In the presence of this pattern, we can designate it as Moyamoya disease (MMD) when it is found isolated in patients with no previously related diagnose (moyamoya primary arteriopathy). If the angiographic pattern is found in association with other neurological or extra-neurological manifestations or an acquired or inherited disorder such as sickle cell disease, neurofibromatosis type 1 or trisomy 21, it is named Moyamoya syndrome (MMS).[13,14,16] Theoretically, the angiographic findings are bilateral in MMD, although severity can vary.[16] When used in isolation, the term Moyamoya refers to the angiographic pattern mentioned above.

This arteriopathy can be categorized in 6 stages defined in 1969 by Suzuki and Takaku that go from narrowing of the ICA apex to the appearance of Moyamoya collateral vessels and finally to occlusion of the ICA and disappearance of the collateral vessels (Table 1).[15,17] As most cases belong to stage III, it was divided in 3 sub-stages (Table 2).[18,19] Children frequently progress through the different stages, while adults often have a steady course of the disease, remaining in the same angiographic stage.[19]

Table 1. Angiographic stages of Moyamoya according to Suzuki classification[15,17]

Stage	Definition
I	Narrowing of ICA apex
II	Appearing of moyamoya collateral vessels
III	Progression of ICA occlusion with intensification of moyamoya collateral vessels
IV	Development of ECA transdural collateral vessels
V	Progression of ECA collateral vessels and reduction of moyamoya collateral vessels
VI	Total occlusion of ICA and disappearance of moyamoya collateral vessels

Abbreviations: ICA, internal carotid artery; ECA, external carotid artery

Table 2. Sub-staging of Stage III of Suzuki's classification[18]

Stage	Definition
III A	Partial non-filling of ACA and MCA
III B	Partial preservation of ACA and MCA
III C	Complete lack of ACA and MCA

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery

6.1.2. Epidemiology

MMD is responsible for approximately 6% of all causes of pediatric ischemic stroke and it is the most common cause of pediatric cerebrovascular events in Japan.[15,20] Although MMD can be found in all ethnicities, it is far more common in Asian countries, with a ten times higher occurrence there than in Eastern countries. Its prevalence is higher in Japan.[14] MMD has a bimodal age distribution with the first peak around the age of 5 and the second around the age of 40.[15,16,19,21] This condition is nearly twice more frequent in female patients that in males.[14–16,19,20] Family history is present in 10 to 15% of Japanese cases and 6% in North American series.[14,16]

As MMS is related with a heterogenous group of diseases, its prevalence and incidence are in line with the associated conditions. It is more common than MMD in European and North American populations. However, in East Asian populations, the incidence and prevalence of MMD is ten times higher than MMS.[13] MMS has a higher incidence in patients with neurofibromatosis type 1, sickle cell disease and Down's syndrome and a great part of these patients are diagnosed in their late teenage years and also in

adulthood.[19]

6.1.3. Genetics and Pathophysiology

The ring finger protein 213 (*RNF213*) gene, located in chromosome 17q25.3, has been identified as a susceptibility gene for MMD.[22,23] Further studies have demonstrated that the heterozygous c.14576G>A variant raises the risk of this condition. Also, when in homozygosity, it is associated with an earlier age of onset, more frequent occurrence of infarctions as initial presentation and increased risk of posterior cerebral artery (PCA) involvement. In the study by Miyatake et al., 60% of homozygous c.14576G>A cases were diagnosed with MMD before completing 4 years of age and the totality of them had infarctions as initial presentation. Therefore, this variant is associated with more severe and broader cerebral vasculopathy. It has been shown that in the presence of this variant, the risk of being diagnosed with MMD is 78%. Furthermore, the c.14576G>A variant could explain the higher prevalence of MMD in East Asian countries, as it has been found in patients from Japan, Korea and China. Some other variants have been identified, though in a much lower frequency.[22]

The knock-out of the *RNF213* gene in zebrafish led to abnormal crop up and irregular diameter of intracranial vessels, which can explain the pathophysiology of this disease in individuals with this mutated gene.[22] However, further studies in RNF213-deficient mice disclosed no changes in cerebral vessels under physiological conditions.[14]

Two missense variants in *RNF213* gene have been discovered in a European family with MMD. These variants are located in the C-terminal portion of the RNF213 protein, just like any other variants reported.[24] There is an increasing evidence of the association of some rare *RNF213* missense variants with Moyamoya angiographic pattern in patients of European ancestry, all located in the C-terminal of the referred protein. Until June 2017, 9 variants associated with this location and to Moyamoya have been described. These recognized variants raise the question of the benefit of a systematic screening of *RNF213* variants in patients with Moyamoya and their relatives. Nevertheless, the struggle in establishing casualty in these variants when founded isolated and the low penetrance observed in many families, make genetic counseling a difficult task.[25]

HLA-DRB1*13 has been associated with MMD both in a Korean and a European study. As HLA expression is related to autoimmunity, a few studies have revealed a higher

prevalence of autoimmune diseases, such as diabetes mellitus type 1 and thyroid disease in MMD patients.[14]

Although fibroblast and hepatocyte growth factors, two angiogenic factors, were overexpressed in patients with MMD and proven not to be simply related with brain ischemia, their coding genes polymorphisms were not proven to be correlated with the occurrence of MMD.[14]

Moyamoya collateral vessels result from dilation of already existing vessels and development of new ones. This leads to a fragile network of vessels with a thin media, a fragmented elastic lamina and microaneurysms with a greater risk of rupture. All this process can be due to abnormal neoangiogenesis in MMD or it can be the result of the production of pro-angiogenic factors by the ischemic cerebral parenchyma.[14]

6.1.4. Presentation

The signs and symptoms can be divided into two groups: (1) ischemic injuries, such as transient ischemic attacks (TIAs) and AIS, and (2) those related to ischemia compensatory mechanisms, leading to hemorrhage from the fragile collaterals or headache by dilation of transdural collaterals.[13,15]

TIAs are defined as focal deficits of acute onset with full reversal within 24 hours, of presumed vascular origin, without correspondent parenchymal infarct on radiologic images.[3] Although the existence of a history of TIAs is frequent, Moyamoya is usually diagnosed in an episode of acute AIS.[13] It is important to note that both adults and children commonly present with ischemic symptoms. Hemorrhage presentation is 7 times more frequent in adults than in children, in which it is rare (2.8%). Children's most frequent presentations are AIS or TIAs (68%).[16,19] Although rare, if there is any hemorrhage presentation in children, it occurs later in the evolution of the disease, probably in the teenage years.[19] These children are often in Suzuki stage III or IV.[26]

A typical manifestation of AIS is the common presentation of this pattern: headache (migraine-like), or other signs of anterior circulation ischemia such as aphasia, dysarthria, hemiparesis, and seizures may be observed. Also, it can sometimes present as syncope, visual changes, or chorea. These symptomatic episodes are likely caused by hyperventilation with vasoconstriction induced by diminished partial pressure of carbon dioxide; so, they can occur by crying or physical exertion. Moreover, hypoxia, hypotension,

hypo-carbic states and hyperthermia increase the risk of ischemic events.[13,19]

Some children may be asymptomatic. However, there is usually progression with ischemic episodes in childhood, even if patients were asymptomatic at first.[13]

6.1.5. Screening and Diagnosis

The initial steps of screening are directed to the diagnosis of MMD and should also identify possible comorbidities that determine the presence of MMS. There may be some clinical clues, such as migraine-like headache, headache associated with focal neurological deficits (as hemiplegia or hemisensory attacks), TIAs, seizures, choreiform movements and characteristic worsening of the symptomatology with hyperventilation.[26]

Any child with confirmed or suspected stroke must undergo further imaging studies to access the possibility of vasculopathy. MRI (Magnetic Resonance Imaging)/MRA (Magnetic Resonance Angiography) has high accuracy to detect small strokes and hemorrhages, and to evaluate basal vascular anatomy. It has an additional advantage, which is the lack of radiation exposure. MRI diffusion-weighted imaging is valuable to identify acute strokes and fluid-attenuated inversion recovery (FLAIR) sequence can be helpful to detect previous events of stroke as regions of reduced cortical blood flow – the leptomeningeal ivy sign.[26] This sign is present in approximately half of the hemispheres involved and in one third of the asymptomatic MMD patients.[27]

Cerebral angiography (CA) is the gold standard to achieve this diagnosis. Three angiographic criteria define the diagnosis of Moyamoya [28]:

1. Stenosis or occlusion of the terminal portion of the intracranial ICA, or proximal segments of the proximal ACA and/or MCA.
2. Presence of abnormal vascular networks near the occlusive or stenotic lesions in the arterial phase.
3. The findings of the previous 2 statements must be bilateral.

As it is an invasive diagnostic method, CA can be replaced by MRA or MRI if the following criteria are present [28]:

1. MRA showing stenosis or occlusion of the terminal portion of the intracranial ICA, or proximal segments of the proximal ACA and/or MCA.

2. MRA showing abnormal networks in the basal ganglia/MRI showing 2 or more visible flow voids in basal ganglia, representing an abnormal vascular network.
3. The findings of the previous 2 statements must be bilateral.

Perfusion-weighted imaging (PWI) and Computed Tomography (CT) perfusion have been useful both in pre and postoperative evaluation of these patients. In a primary approach, CT perfusion scan can identify areas of recoverable ischemic brain probably eligible to revascularization procedures.[19] Cerebral blood flow (CBF) can be assessed by Single Photon Emission Computed Tomography (CBF-SPECT) and Positron Emission Tomography (PET). CBF is relevant not only for diagnosis and staging of MMD, but likewise can represent an indication for revascularization surgery when diminished.[21]

Several studies were developed to find a suitable biomarker to diagnose MMD. Recently, four exosomal microRNAs were identified in cerebrospinal fluid as possible biomarkers for this disease. However, further investigation and larger patient cohorts are necessary to evaluate their accuracy.[29]

6.1.6. Treatment

The purpose of treatment in symptomatic patients is to prevent further worsening of their clinical condition by ischemic and/or hemorrhagic events.[26]

Medical therapy is generally considered inefficient. Acetylsalicylic acid, steroids, vasodilators, antibiotics, low-molecular-weight dextran, mannitol and intravenous (IV) infusion of calcium-channel blockers, such as verapamil, nimodipine and nicardipine, have been tested with no validation or success, as they do not change the natural progression of the disease.[19,30] Thus, they can be considered only as part of the acute management and secondary prevention of stroke and also in poor surgical candidates.[26] Therefore, surgical revascularization techniques along with anti-platelet therapy management and permissive hypertension are the preferable choice for both treatment and secondary prevention in patients with symptomatic MMD.[30]

Revascularization techniques can be divided into three groups: direct revascularization procedures, indirect procedures and combined strategies.[21,26,30] These procedures aim to reverse or stop any existing ischemia or abnormal angiogenesis by offering an alternative pathway to cerebral perfusion.[30] Direct revascularization consists in a vessel-to-vessel anastomosis between a branch of the external carotid artery (ECA) –

usually the superficial temporal artery – and the ICA or the MCA. It is the ideal option when immediate reperfusion is necessary. However, it is a challenging surgery in younger children, as they have thinner and more friable arteries than adults. These procedures are used with the purpose of revascularization of MCA branches and are not usually performed when the affected branches are from the ACA or the PCA. Indirect revascularization uses a vascularized pedicle graft from the ECA to promote angiogenesis by placing it over the surface of the brain. This is a less complex and faster procedure and has a clear advantage: it can be applied in the ACA and PCA territories. Various surgical options can be considered, such as encephalo-duro-arterio-synangiosis and encephalo-myo-synangiosis. Combined revascularization can use direct and indirect techniques or two or more indirect techniques. In children, two indirect techniques combined have proved their benefit, safety and feasibility.[26]

In the perioperative period, it is important, both on MMD and MMS, to pay close attention to patients' hemodynamics, such as blood oxygenation and levels of CO_2, and to correct their levels if necessary, to prevent any intraoperative ischemia. Fluctuations on these parameters must be avoided. It is also important to maintain normotension and euvolemia. These factors can affect the diameter of the cerebral vessels, leading to decrease blood flow, which can result in cerebral ischemia.[26]

When direct revascularization is performed, its effectiveness can be evaluated by cerebral hemodynamics on CT perfusion scan. Transcranial doppler (TCD) is also an option to assess the success of the revascularization by comparison between the mean arterial velocity and resistance index before and after surgery. Furthermore, serial TCD can be performed in the postoperative period to establish an improved blood flow, meaning a successful revascularization procedure.[19]

6.1.7. Prognosis

The evolution of this disease, whether it is MMD or MMS, is unpredictable. However, it is known that the arteriopathy and the associated clinical symptoms will progress in untreated patients.[16] In fact, no matter the etiology, this condition will worsen in almost all individuals and more than two-thirds of patients will have symptomatic progression within 5 years, leading to permanent neurological deficits or death without treatment. The most important predictor of outcome is the patient's neurological status at the time of treatment.[31] Moreover, it has been stated that the presence of irreversible infarction is the highest risk for

poor outcome.[22]

Revascularization surgery is known to be a safe and effective treatment for MMD. If performed before significant damage, it improves quality of life, cognition, prevents neurocognitive impairment and influences the evolution of the disease.[26] It has been demonstrated that combined bypass surgery has better outcomes than indirect methods. Moreover, both direct and combined bypass surgeries have shown to be superior on the development of collateral vessels.[32]

6.1.8. Moyamoya Syndrome (MMS)

MMS can affect anterior and/or posterior circulation, unilaterally or bilaterally. As it may be associated to a heterogenous group of conditions, it also has several different clinical presentations, patterns of inheritance and penetrance of Moyamoya angiopathy, between the different inherited syndromes.[14]

MMS and Sickle Cell Disease

Sickle Cell Disease (SCD) is an autosomal recessive hemoglobinopathy derived from a mutation of the *HBB* gene located in chromosome 11, which encodes the ß subunit of the hemoglobin molecule. SCD happens when there are two mutated *HBB* alleles. This leads to erythrocytes containing hemoglobin S, which forms insoluble aggregates when in low oxygen tension. Consequently, red blood cells (RBCs) become rigid and sickle shaped, with higher fragility and propension to adhere to the endothelium of blood vessels, especially in the microvasculature, causing occlusion. Hemolysis and the recurrent cycle of ischemia-reperfusion, together with chronic inflammation, eventually lead to vaso-occlusive crises and vasomotor dysregulation. Blood stasis will potentiate platelet adhesion and fibrin deposition, which will ultimately cause severe narrowing or even occlusion of important major vessels, for example, cerebral vessels.[33,34]

It is mostly seen in people from sub-Saharan Africa, Middle East and India, who migrate to America and Western Europe. In some African countries, 10-40% of the population carries this gene variant. One in 365 born African Americans has SCD and 1 in 13 has sickle cell trait.[14,33]

Its clinical presentation is composed by chronic hemolytic anemia, painful vaso-occlusive crises and multiorgan involvement, such as the brain, heart, lungs, eyes, liver, gallbladder, spleen, kidneys, bone and others. Symptomatic stroke is one of the most devastating complications of SCD, and it happens in 1 in 10 children. However, heterozygous individuals – sickle cell trait – are classically asymptomatic, although they can present fatigue, hematuria, and rhabdomyolysis when in extreme conditions.[33]

Intracranial occlusive disease in SCD can lead to a Moyamoya pattern, developing MMS in 30-40% of the patients, mainly in children and young adults. Just like MMD, ICA, ACA and MCA are the most affected arteries. Stroke is a major cause of morbidity and mortality in SCD. According to the Cooperative Study of Sickle cell disease, an observation study that supervised a cohort of 4082 adults and children over 5 years, the prevalence of stroke was 3.75% with two peaks of prevalence: between the ages of 2 and 5 years and between 40 and 49 years old. In this pediatric peak, ischemic strokes were the most common.[33]

Hemoglobin electrophoresis is the key to diagnose SCD. TCD is used to measure mean blood flow velocities through large intracerebral arteries, which increase when there is stenosis of the vessels, and constitutes the screening test to evaluate the risk of stroke. CT utility is in acute stroke cases, to search for cerebral hemorrhage. MRI provides additional information concerning acute and chronic ischemic areas. MRA and CT angiography may identify Moyamoya pattern, although a subtraction angiography will be necessary to assess this possibility.[33]

Management of AIS in SCD requires immediate exchange transfusion to diminish the percentage of hemoglobin S to less than 30% and rise tissue oxygen delivery with the non-sickle RBCs. This may be achieved with erythrocytapheresis or simple transfusion.[33] The current evidence is inconsistent when choosing the best surgical procedure in MMS with SCD. However, indirect revascularization procedure has been the most used in these patients, which can be related to the challenges of performing direct revascularization techniques in pediatric patients.[35] In the United States of America (USA), about 90% of people who suffer of SCD survive to adulthood. Yet, in low-income countries, the amount of children who live into adulthood is lower than 10%.[33]

MMS and Neurofibromatosis type 1

Neurofibromatosis type 1 (NF-1) is an autosomal dominant genetic neurocutaneous condition. It is caused by germline loss of one *NF1* allele, which protein – neurofibromin – is expressed in vascular endothelial cells and smooth muscular cells. *NF1* is a tumor suppressor gene that inhibits cell cycle progression, located on the long arm of chromosome 17 (17q11.2). Therefore, the loss of this gene can result in inappropriate proliferation of the cells in which it is expressed.[36,37] It is important to note that no connection between *NF1* genotype and MMS phenotype was found. However, NF-1 might be a predisposing factor for MMS, but genetic modifiers unlinked to NF-1 may also play an important role in MMS pathogenesis.[38]

MRV11 gene has also been implied in the pathogenesis of MMS in NF-1 patients. It might represent a genetic susceptibility factor for MMS in these patients. *NF1* mutations lead to vessels predisposed to stenosis after damage and the simultaneous occurrence of the p.(P186S) substitution identified in *MRVI1* can be a trigger in this scenario, impairing arterial relaxation.[37]

This disease's approximate incidence is 1:3000. Although the prevalence of NF-1 is constant worldwide, MMS related to NF-1 has been described mostly in Caucasians in Europe and in the USA instead of Asians, in opposition to MMD. Moreover, there is no ethnic predisposition to NF-1.[37] NF-1 can affect multiple organs, including the brain, peripheral nerves, eyes, skin and bones. Optic glioma, macrocephaly, learning and cognitive disabilities are some of the possible findings. Some patients develop cerebral vasculopathy, which comprehends stenosis/occlusion and aneurysmal dilation. Stenosis/occlusion is the most common form found in children (Fig. 1).[36] Although some authors referred MMS was more common in patients with optic glioma, those conclusions could be biased due to the high frequency of MRI screening in these patients, since other studies found no correlation between these two features. A correlation between Suzuki's grade of MMS and symptoms has been suggested.[38]

MMS is the most common cerebral arteriopathy in NF-1, with an occurrence of 2 to 6% in NF-1 patients, with a larger risk in patients undergoing cranial irradiation.[37] In a surgical series of NF-1-associated MMS patients, 62% had bilateral vasculopathy and 76% were symptomatic.[36] Routine MRI screening can help in early detection of cerebral vasculopathy in NF-1 patients before they become symptomatic. This screening is controversial. Current guidelines for diagnosis of NF-1 do not support routine neuroimaging in asymptomatic individuals. Patients should be clinically monitored to detect symptoms

related to cerebral vasculopathy. If symptomatic, they should undergo MRA. However, some authors have advocated for this screening, so that an early diagnosis can be made, in order to achieve better clinical outcomes.[36,39]

Most patients of the studies already conducted in this area were asymptomatic and had unilateral vasculopathy. Surgery in these patients was reserved to symptomatic or progressing patients. Previous cranial irradiation has been associated with new episodes of infarctions after surgery.[36]

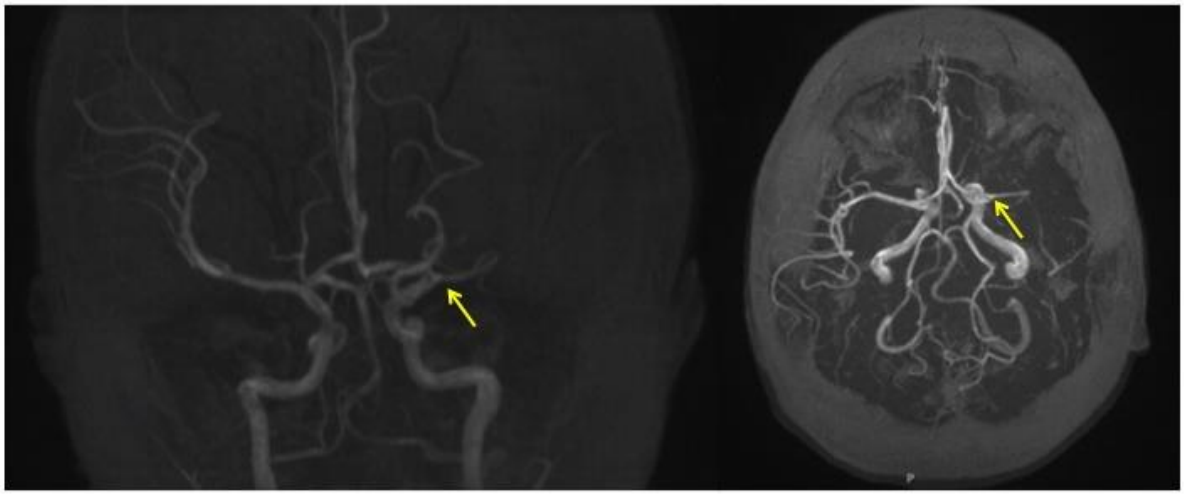

Figure 1. MRA showing stenosis (arrow) of the M1 segment of the left MCA in an adolescent with NF1, regularly observed in the Neurology consultation (Hospital Pediátrico). Differences in the flow detected in the vessel are evident, when compared to the contralateral MCA. These are changes that precede MMS development.

MMS and Down Syndrome

Down Syndrome (DS) is the most frequent chromosome disorder in live born children. In the USA, it exists in 1/700 births. It is caused by the existence of an extra inherited chromosome 21. DS, or trisomy 21, is commonly related to a high rate of congenital heart disease and is also associated with endocrine disorders, severe development delay and gastrointestinal malformations, such as duodenal atresia.[40,41] Classical characteristics include facial features, such as upward slanted palpebral fissures, epicanthal folds, and a rounded, flattened face.[42] These patients may also have multiple neurologic manifestations, such as MMS, cervical spinal cord compression by atlantoaxial subluxation, and basal ganglia

damage. Still, the association of these neurological conditions simultaneously is rare. Patients with DS may present with epileptic seizures, stroke and dementia.[43]

Moyamoya has a higher frequency in DS than in the general pediatric population.[41,42] Among the patients with Moyamoya, DS has a prevalence of 3.8%. In a 2015 study, MMS in DS was diagnosed at an older age than in non-DS Moyamoya (8.4 years vs. 6.5 years, respectively) and also the entire MMS in DS group presented with symptoms vs. 75% of the non-DS Moyamoya group. All the patients with DS presented with ischemic strokes and 26% of them had had seizures prior to diagnosis. Ninety seven percent of the patients with DS had radiographic signs of stroke prior to surgery.[41]

The pathophysiology of vascular occlusion in DS associated with MMS remains unknown. However, these patients are predisposed to several vascular abnormalities as many proteins related to augmented risk for vascular disease have genes located on chromosome 21.[43] Therefore, vascular dysplasia and autoimmunity mechanisms have been proposed as potential explanations for these events.[44]

As these patients may have strokes caused by embolic events due to their cardiac disease, the diagnosis of MMS linked to DS may be delayed. Therefore, some authors recommend the use of MRI/MRA in order to determine the occurrence of stroke and also to evaluate the presence of Moyamoya.[41]

Regarding treatment, it is important to have a multidisciplinary approach, as these patients' multiple disorders make it essential to reduce anesthetic and perioperative risks.[41] The indirect revascularization procedures are the most used in DS-MMS patients.[42] In the mentioned 2015 study, the DS-MMS patients had no new stroke events after hospital discharge, contrary to non-DS patients, although there was progressive arteriopathy in 81% of them.[41] In another DS series, good recovery after surgery was seen in 53% and fair recovery with persistent neurologic deficit in 40% with the remaining 7% having poor outcome, with declining neurologic status.[42]

6.2. *ACTA2* Variants-Associated Disease

6.2.1. Etiology, Pathophysiology and Presentation

ACTA2 gene, located on 10q22-q24, encodes alpha-smooth-muscle-actin, an important component of the contractile units of vascular smooth-muscle cells (SMCs).[45] *ACTA2* pathogenic variants lead to a gain of proliferative function of SMCs, resulting in occlusion of small arteries, as they are deficient in elastin, an important inhibitor of SMC proliferation. Larger arteries appear to be susceptible to aneurysmal disease, possibly as a result of loss of contractile function.[1] The transition from dilated to normal/stenotic arterial caliber in ICA coincides with the cavernous portion of ICA, the location of the transition from an elastic to muscular artery.[46] This fact supports the hypothesis of the influence of arterial wall components, particularly the presence or absence of elastin, in the abnormal SMCs proliferation by *ACTA2* variants.[45,46]

The p.Arg179His heterozygous variant is associated with an early onset severe phenotype caused by global smooth muscle dysfunction, including aortic and cerebrovascular disease, persistent ductus arteriosus (PDA), aortopulmonary window (APW) and dysfunction of organs dependent on smooth-muscle function, presenting as congenital fixed mydriasis, hypotonic bladder, intestinal malrotation and hypoperistalsis, and pulmonary hypertension.[1,46–48] The set of these manifestations is denominated Multisystemic Smooth Muscle Dysfunction Syndrome (MSMDS).[47] Arg179Leu, Arg179Ser and Arg179Cys variants have also been reported to have a similar phenotype.[46,49] Pulmonary arterial hypertension associated with PDA or APW, asthma and chronic lung disease have been reported in these patients. The exact pathophysiology of this chronic lung disease is not clear, but it may be associated with a developmental defect in lung parenchyma predisposing to emphysema.[48]

Variants involving Arg179 seem to cause the most severe cerebrovascular disease and multisystem phenotype. Evidence of small vessel disease, such as high degrees of periventricular and subcortical white matter leukoariotic changes, have also been reported. This phenomenon is hypothesized to be age related.[46] However, there have been reported 2 cases of neonates already presenting these white matter changes.[50]

This mutation has been previously associated with MMD. However, there are distinctive features between these two entities, as cerebrovascular disease caused by *ACTA2* variants presents with a combination of arterial ectasia and stenosis and abnormally

straight arterial course, particularly in the circle of Willis; absence of basal collaterals; and more widespread cerebrovascular involvement.[46]

Variants of the arginine at position 258 (p.R258C and p.R258H) have been described as having a severe presentation with an increased risk for aortic dissection and a high risk of stroke. The cerebrovascular phenotype is like the associated with variants of arginine at position 179, but the abnormally straight arterial course may not be present. Evidence of small vessel disease and cerebral ischemia were also found in patients with these mutations, along with anomalies of the intracranial ICA and vertebrobasilar arteries. Both arginine variants at positions 258 and 179 cause similar types of functional defects, but p.R179 causes a more severe impact. This has been demonstrated in an *in vitro* assay.[47]

Alpha-actin is not expressed in brain parenchyma, but solely in vessels. Therefore, it is not likely that a pathogenic variant affecting this isoform would have a direct influence in brain development. However, it is possible that cross-regulation between different isoforms may influence patients with *ACTA2* variants. Actually, some parenchymal malformations, probably due to the increased rigidity of the intracranial vessels, have been described in the corpus callosum, anterior cingulate gyrus, frontal gyrus, fornix, pons and midbrain.[45,51] Epilepsy in these patients is rare, except if associated with brain ischemia, and intellectual outcomes seem to be associated with brain ischemia, rather than with isolated brain malformations.[45]

Recently, a new heterozygous pathogenic variant in *ACTA2* gene has been described – p.(Asp181Val) – in a Portuguese patient with cerebral arteriopathy and brain malformations (Fig. 2).[51]

A case of a pregnant woman diagnosed with MSMDS during pregnancy has been reported. Fetal ultrasound showed some abnormalities and testing after birth confirmed the inheritance of the *ACTA2* variant from the mother. Also, while performing the planned cesarean section at 37 weeks of gestation, an atonic uterus and friable tissues were found.[48]

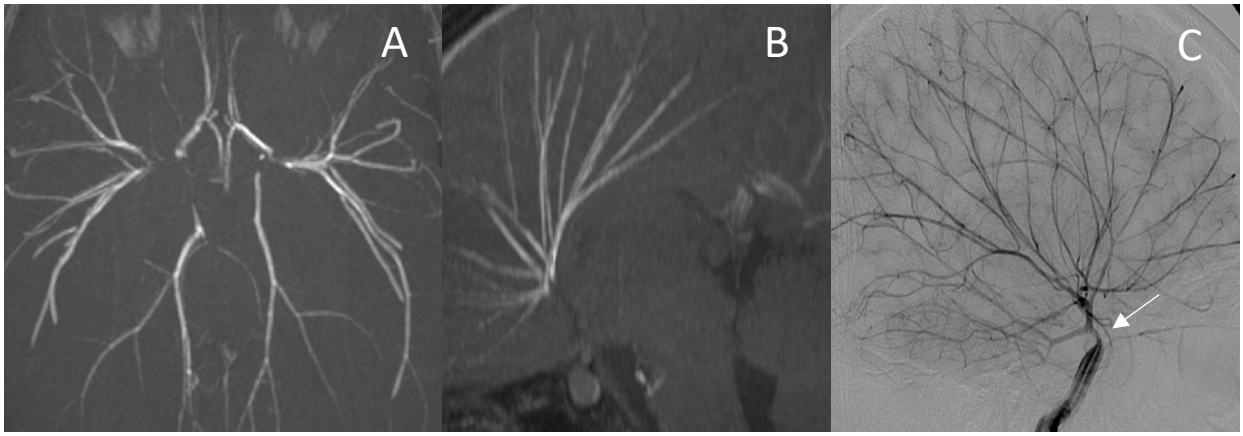

Figure 2. MRA (A – axial and B – sagittal reconstructions) and digital subtraction angiography (C – lateral view of internal carotid artery) showing diffuse straightening of cerebral arteries in a "twig-like" pattern, without Moyamoya vessels, in a Portuguese adolescent diagnosed at Hospital Pediátrico. Stenosis of distal internal carotid arteries was also seen (C – arrow). [51]

6.2.2. Epidemiology

In a study with a cohort of 33 patients diagnosed with MSMDS, the median age of them was 12 years old and the median age at diagnosis was 11 years old. Also, 36% were males and 64% were females. The majority of these patients (26) were of European ancestry, 5 were Asian, 1 was African-American and 1 was Hispanic.[48,52]

6.2.3. Diagnosis

Neurologists, neuroradiologists and vascular medicine specialists may see some signs of *ACTA2*-related disease that can serve as a diagnostic clue, in addition to family history.[47] Fixed dilated pupils in a young age are extremely rare. Therefore, this finding should alert pediatricians and ophthalmologists to the possibility of the coexistence of a systemic disorder, such as MSMDS.[53] An ophthalmologist must do a complete eye examination, including funduscopic examination.[48] Patients presenting with PDA or APW or congenital mydriasis or related pupil abnormalities, including newborns, should be referred to a geneticist for evaluation and be genetically tested for an *ACTA2* variant.[48,53] Due to the presence of congenital mydriasis and PDA, these patients are usually evaluated with brain MRA, although conventional angiography is the definitive imaging modality.[1] White matter

abnormalities are usually described as having an increased T2 signal intensity on MRI in the periventricular white matter. MRI can also show brain malformations.[54]

Therefore, a baseline brain MRI and head and neck MRA should be performed, as these exams can also help in accessing the future risk of stroke and in the management to prevent neurologic complications. Conventional angiography should be reserved for patients with focal neurologic symptoms or when there's evidence of critical or progressive narrowing of cerebral vessels in MRA or TCD. At the time of diagnosis, the entire aorta must be evaluated. Follow-up imaging by echocardiography or cardiac MRI/MRA with cardiac-gated sequences should be performed. This surveillance should start by the age of ten or earlier if there were anomalies in the initial evaluation.[48]

6.2.4. Treatment

As in Moyamoya, prevention of AIS consists in antiplatelet agents or surgical revascularization.[1,46] Acetylsalicylic acid may be used as primary prevention for stroke, but carefully due to the risk of Reye syndrome.[48] Inhibitors of the abnormal SMC proliferation, as imatinib, have been suggested as a possible measure to prevent disease progression.[1,46] Most patients with PDA require surgical correction in the first year of life. Untreated PDAs lead to progressive respiratory deterioration, prolonged ventilator support and death. Delay of this procedure can worsen the pulmonary artery hypertension.[48]

These patients may benefit from treatments such as beta-blockers and losartan that slow aortic growth and prevent aortic dissection. Due to the hypotension and cerebrovascular disease in these patients, this treatment must be started with low doses and close monitoring of blood pressure and symptoms. Elective surgery must be considered, but it is important to consider its risks and benefits due to the existing cardiac, cerebrovascular and pulmonary conditions. Pulmonary comorbidities may require oxygen supplementation, bronchodilator or anti-inflammatory agents. Intestinal malrotation may require surgical correction. Laxatives may be used when there's constipation due to gut immotility. Gastric or nasogastric tube feeding may be necessary if there are feeding difficulties and failure to thrive. Hypotonic bladder may be managed with increase fluid intake, techniques or drugs to trigger voiding, or surgery. Standard anticonvulsant therapy is used in the management of patients with seizures.[48]

6.3.5. Prognosis and Follow-up

A multidisciplinary approach is necessary in patients with this syndrome, as some medications and procedures used to treat one complication may worsen disease in other systems.[48]

Patients should be monitored for aortic disease that can develop later and be life-threatening.[46] There is a higher rate of postoperative AIS in children with p.Arg179His variant undergoing revascularization surgery, when compared with Moyamoya.[1,46] Besides this, a propension to recurrent AIS and progressive brain injury has also been reported.[46] A periodic screening for cerebrovascular disease should be part of these patients' surveillance. This can be done with TCD.[48]

Routine cognitive and psychological evaluation should be done to evaluate the need of further neurologic evaluation, rehabilitation and modifications at school or home. In a 33 patients' report, a higher risk of death has been identified in patients under 18 years and over 30 years old. Dead occurred due to aortic dissection, post-operative complications of aortic surgery, stroke, or pulmonary complications. The age of the oldest living patient in this cohort was of 37 years old.[48]

Patients must be offered genetic counseling to assess concerns about inheritance, recurrence risk and reproductive options.[48]

6.3. Grange Syndrome

Grange Syndrome (GS) is a rare autosomal recessive condition characterized by severe early-onset vascular disease.[55]

6.3.1. Etiology and Pathophysiology

Homozygous loss-of-function variants of *YY1AP1* gene have been identified as the genetic etiology of GS. YY1 associated protein 1 (YY1AP1) is the product of this gene and has been recognized as an activator of the transcriptional activity of YY1. Both YY1AP1 and YY1 have been identified in the nucleoplasm of smooth muscle cells (SMCs), but only YY1AP1 was identified in the nucleolus. These have been detected in SMCs of some arteries. Loss of *YY1AP1* diminishes both differentiation and cell proliferation of SMCs, hypothesizing its role in arterial stenosis and aneurysms.[55]

6.3.2. Presentation

GS is characterized by hypertension and multifocal steno-occlusive lesions of renal, cerebral and abdominal arteries. Bone fragility, syndactyly, brachydactyly, congenital heart defects and learning disabilities are some of the features related to this syndrome associated with different expressivity and incomplete penetrance.[56] This multifocal vascular disease associated with GS may be accompanied by renovascular hypertension and fibromuscular dysplasia.[57] Stenosis of vertebral arteries, ICA (Fig. 3), MCA and PCA, lesions in the periventricular white matter suggesting small vessel ischemic disease, occlusive lesions of superior mesenteric and celiac arteries leading to bowel ischemia, narrowing of external iliac arteries, stenosis of renal arteries, coronary artery disease, patent ductus arteriosus, bicuspid aortic valve, long QT syndrome, aortic aneurysm, mild facial dysmorphia are some of the features described in association with loss-of-function variants of *YY1AP1* gene.[55] Some symptoms may present only after adolescence.[57]

GS has a common feature with MMD as the intracranial location of the cerebrovascular occlusions and the collateral vessels formed at the base of the brain are similar.[55] ICA stenosis is a regular feature of GS, usually identified in the second decade of

life. Some authors highlight that bilateral ICA stenosis, hypertension and renal arteriopathy are its classic phenotype and, on the other hand, bone fragility, intellectual disability and congenital heart defects are not, representing the variable characteristics of GS.[56]

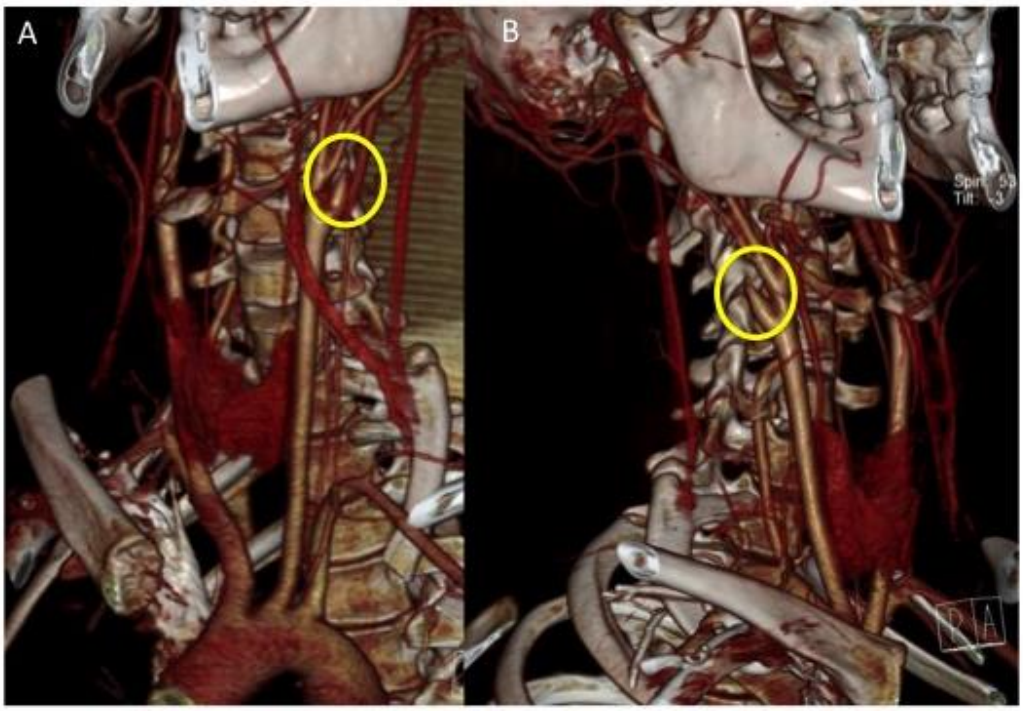

Figure 3. Reconstruction of a cervical angio-CT scan of a patient diagnosed with GS at Hospital Pediátrico. The image shows a bilateral occlusion of the internal carotid arteries (A - left; B- right), with the yellow circle highlighting the typical pencil point image that can be identified in these situations.

In a recent research project, 10 out of 11 patients had cerebral artery stenosis (81.8%) and strokes were registered in 54.5% of them. It must not be forgotten that pediatric hypertension is usually asymptomatic, but can also lead to hypertensive emergencies, such as hemorrhagic stroke. Chest or abdominal pain must be managed as urgent, as they are indicative of the onset of ischemic events.[57] Heterozygous carriers of pathogenic germline variants are commonly asymptomatic.[56]

6.3.3. Diagnosis and Follow-up

As there are multiple presentations of GS, genetic analysis of *YY1AP1* gene may be necessary to confirm the diagnosis. At-risk relatives of GS patients can be advised to have regular, noninvasive medical examinations.[56] Pediatric follow-up examinations are needed in GS.[57] Since it is a very rare condition, with very few cases described worldwide, it is difficult to establish prognostic considerations in GS.

6.4. Menkes Disease

6.4.1. Definition and Presentation

Menkes disease (MD) is a rare early-onset (6 to 8 weeks of age) X-linked recessive metabolic disturb caused by mutations in the *ATP7A* gene.[58–60]

MD shows much clinical heterogeneity, even in progression and severity of neurological symptoms and age of death. In fact, most patients suffer from the classical form, which results in death in early childhood, mostly before the age of 3. On the other hand, some patients have severe symptoms but survive longer, therefore being called long-surviving MD patients.[61] The mildest form of MD is Occipital Horn Syndrome (OHS) in which neurological symptoms are less severe and the symptoms are predominantly from the connective tissue, such as hyperextensible joints and skin. These patients also present with dysautonomia and may present with bladder diverticulae.[61,62] The major distinction between these two is the radiographic presence of the occipital horns – symmetric exostoses protruding downward from the occipital bone. There have been described about 5-10% MD patients with intermediate phenotypes, but these forms are not well categorized and have been differently named.[61,63]

MD clinical features go from seizures to hypotonia, failure to thrive, hair (short, sparse, coarse, twisted and often lightly pigmented – *pili torti*) and connective tissue abnormalities, such as *cutis laxa* and hyperextensible joints, temperature instability and early death, commonly before three years of age. Osteoporosis, syncope, vascular tortuosity, bladder diverticulae, diarrhea, gastric polyps, pectus excavatum, umbilical or inguinal hernias and distinctive facial features, such as jowly appearance with sagging cheeks, have also been reported.[60,62,64] Drug-resistant epilepsy appears in the first three months of life.[59] Occipital horns have not been described in the neonatal period in MD patients, but may appear after 2 years of disease progression or in long term surviving patients who receive parenteral copper-histidine, although not all treated patients develop occipital horns.[62] Pneumonia often precipitates respiratory failure, which is a common cause of death.[64]

Subdural hematomas and cerebrovascular accidents are common.[64] Also, in late phases of MD, diffuse cerebral and cerebellar atrophy, neuronal loss, gliosis within cortical and deep gray matter, loss of Purkinje cells, cerebral white matter spongy changes along with loss of myelin sheaths and axons, and thin-walled and strikingly tortuous intracranial

arteries may be present. Increased artery tortuosity is considered a typical diagnostic feature of MD, described in about 75% of cases. Whether it is present since birth as a stable feature or it progresses, eventually leading to blood supply abnormalities, remains unknown.[59] Basal ganglia lesions are also reported in children with MD and they are typically bilateral, but asymmetric.[58]

The presentation in affected females is usually milder than in males of the same family and they also survive longer.[61] Actually, heterozygous females are thought to be asymptomatic, but half of them have regions of *pili torti*. Scattered hypopigmentation has also been reported. Seizures and abnormal neuroimaging findings, such as cerebrovascular tortuosity and cerebral atrophy, have been described in 11 of 18 females that enrolled in a recent study.[65] Few cases of classical MD have been reported in females.[65,66]

ATP7A mutations have also been associated with ATP7A-related distal motor neuropathy (ATP7A-related DMN) which may also start in childhood, but it is usually diagnosed in adulthood, given its slow progression. Distal lower limb weakness and gait instability are its main features, associated with distal muscle wasting and foot deformity with normal, reduced, or absent deep tendon reflexes. Hands may also be affected. There is a reduced number of patients described in the literature, but they do not have skeletal abnormalities, such as occipital horns, nor skin and joints hyperextensibility. Dysautonomia has been described once.[62]

OHS and MD may overlap and OHS and ATP7A-related DMN may also do so.[62]

6.4.2. Epidemiology

Based on loss-of-function variant frequencies in the Genome Aggregation Database, it is predicted that MD's minimum birth prevalence is of 1 in 34 810 live male births.[67] In Europe, MD's overall incidence is of 1 in 300 000 births.[59,61] In Japan, it has been reported to be 1 in 360 000 births. The great majority of patients are males, as expected, although there are also a few female patients described.[61]

6.4.3. Etiology and Pathophysiology

ATP7A gene's location is in the long arm of chromosome X (Xq13.2-q13.3). It

encodes for the trans-Golgi copper-transporter P-type adenosine triphosphatase. When dysfunctional, there is an impaired absorption and cellular metabolism of copper, which leads to an early, serious multisystem disease that usually results in death in early childhood.[58] Three hundred and seventy different variants have been identified in patients suffering from MD. The most common is the p.(Gly727Arg) missense mutation found in 10 patients.[61] It has been reported that 12-20% of MD cases involve copy number variations (CNV's).[67]

The clinical characteristics of MD are the result of malfunction of one or more copper-requiring enzymes, named cuproenzymes, and reduced activity of other enzymes because of the ATP7A deficiency.[61] Some of the affected enzymes are ceruloplasmin, cytochrome c oxidase, tyrosinase, lysyl-oxidase and superoxide dismutase. Also, the ATP7A transporter is necessary for the passage of copper across the blood-brain barrier and, inside the brain, copper is a cofactor of some enzymes, including dopamine-ß-hydroxylase.[68] Copper deficiency leads to diminished activity of lysyl-oxidase, which causes defective cross-linking of elastin and collagen. This along with some contribution from reduced cytochrome c oxidase activity may explain the increased risk of stroke of these patients, as it results in structural impairment of the blood vessel wall.[59,69]

It is thought that due to neutropenia and humoral immunodeficiency associated with copper deficiency, children with MD have a higher susceptibility to recurrent infection. A case of NK cell dysfunction associated with recurrent infections has also been reported, as a result of impaired incorporation of copper on the Golgi complex.[70]

There are some female cases reported, most of them having an X-autosome translocation, truncating ATP7A, leading to clinical manifestations and attributed to random X inactivation.[63] OHS and ATP7A-related DMN are also X-linked recessively inherited.[62]

6.4.4. Diagnosis

Classical MD is only suspected at birth in the presence of family history and is more commonly detected after the onset of symptoms, around 6 to 10 weeks of age. Sometimes, there is a later recognition, between 2 and 10 months of age.[60] Therefore, MD diagnosis is suggested by clinical manifestations and confirmed by the determination of diminished levels of serum copper and ceruloplasmin. Other investigations, such as light microscopy for hair changes or radiography for occipital horns, may be used mostly to determine the presence of

some clinical features.[61] Plasma dopamine and norepinephrine determinations can be used as an alternative diagnostic test, as there usually are high levels of dopamine and low levels of norepinephrine, due to decreased activity of dopamine-ß-hydroxylase. Dopamine:norepinephrine ratios and the ratio of their metabolites has been reported as of high sensitivity and specificity for MD.[68]

The ultimate confirmation of the MD or OHS diagnosis is the identification of a pathogenic variant in *ATP7A* gene.[61]

MRI of MD patients may show defective myelination, atrophy with ventriculomegaly and vascular tortuosity. MRA demonstrates a “corkscrew” appearance of cerebral vessels.[64] Angiography shows extreme tortuosity of cerebral arteries, which usually present as elongated and tortuous with distal narrowing.[1] There are some findings in conventional skeletal radiography, like diffuse osteoporosis, periosteal reaction, metaphyseal spurs, excessive epiphysial spurring leading to fragmentation and fractures and scalloping of posterior border of vertebral bodies.[71]

Females with suspected MD or variant phenotypes should undergo molecular genetic testing, even if serum copper and ceruloplasmin levels are normal, in the context of a high degree of clinical suspicion.[65]

OHS also presents with decreased levels of serum copper and ceruloplasmin than can be as low as in classical MD. ATP7A-related DMN usually has normal or slightly low serum copper levels and electrophysiological studies show signs of peripheral neuropathy.[62]

Some authors have proposed the inclusion of these conditions in the newborn screening test. All infants with *ATP7A* variants found with this method could undergo an assay for plasma catecholamine levels, as both MD and OHS have abnormal plasma catechol profiles. This aims for identifying newborns at-risk to develop these conditions in a pre-symptomatic period.[60] Abnormal plasma neurochemical levels because of the deficiency of a copper-requiring enzyme, dopamine ß-hydroxylase, are diagnostic in affected MD newborns.[67]

6.4.5. Treatment

In most of the cases, the treatment is mainly symptomatic and it has been shown to have an impact in extending survival.[61]

The specific treatment for MD has the goal to offer extra copper to the tissues and the cuproenzymes. Copper administration should be made parenterally or subcutaneously. Copper-histidine has been proven to be the most effective copper compound, although its success depends on early initiation and presence of at least a partially functional ATP7A protein.[61] Adeno-associated virus-mediated *ATP7A* gene therapy appears highly promising as complementary strategy in combination with subcutaneous copper-histidinate, showing a synergistic treatment effect in the Menkes mouse model.[67] Management of MD in females aims to relieve symptoms and there are also targeted interventions in areas of physical and cognitive disabilities.[65]

6.4.6. Prognosis

When not treated, MD progresses with neurological decline starting in early infancy.[60] Early parenteral copper-histidine supplementation may change disease evolution and the long-term outcome of these patients, as there is a milder neurological course. However, this supplementation cannot prevent skeletal abnormalities.[61] Early (by 10 to 28 weeks of age) subcutaneous supplementation for 3 years has also been described with improved clinical outcomes.[60,61] There are also reports of the success of treatment with copper-histidinate started soon after birth or even *in utero*.[69]

Parenteral copper supplementation improves muscle tone and motor activity and also prevents seizures.[70] Indeed, a case of long-surviving adult classical MD patient who tolerated long-term intravenous copper supplementation has been described. This patient had marked skeletal and vascular abnormalities, proving MD as a progressive connective tissue disease, even with copper level normalization. It has been hypothesized that it can be related with the patient's specific genotype.[72]

Early diagnosis of MD in the newborns metabolic screening would improve neurodevelopment outcomes and also abolish the need for uncomfortable and costly interventions and diagnostic tests.[67]

6.5. PHACE Syndrome

The acronym PHACE stands for posterior fossa malformations (P), hemangiomas (H), arterial anomalies (A), coarctation of the aorta and cardiac defects (C), and eye abnormalities (E). The denomination for this neurocutaneous syndrome was proposed by Frieden in 1996. Additionally, when sternal clefting and/or supraumbilical abdominal raphe are present, this syndrome can be denominated as PHACES.[73]

6.5.1. Epidemiology

In a large study with 1096 children with 12 years of age and younger with infantile hemangiomas, 25 (2.3%) met diagnostic criteria for PHACE syndrome. These 25 patients corresponded to 20% of all children with large, segmental facial hemangiomas. Another subsequent study with 108 children with large, segmental facial hemangiomas reported that 33 (31%) met diagnostic criteria for PHACE syndrome. Moreover, children suffering from PHACE syndrome had significantly larger hemangiomas than those without this condition.[74]

The estimated prevalence of PHACE syndrome is less than 1 in 1 000 000.[75] In a small European cohort of patients, female preponderance has been described and a female-to-male ratio of 9:1 had already been reported. However, a larger cohort has established a female-to-male ratio of 4:1.[76,77] This syndrome is more common in Caucasians than in other ethnicities.[76]

6.5.2. Presentation

Malformations of cerebellum and posterior fossa structures are the most common congenital brain abnormalities found in patients with PHACE syndrome.[78] The frequency of posterior fossa anomalies differs in published reports from 30.4% to 81.0%. Cerebral anomalies occur in a lower frequency.[79] The most common structural brain defect in this syndrome is unilateral cerebellar hypoplasia. There are other associated features, such as Dandy-Walker complex, dysgenesis of the cerebellar vermis, hypoplasia of the brainstem and malformations of cortical development. These malformations can lead to focal neurologic deficits, speech delays and/or neurodevelopment impairment.[77] Location-related epilepsy

and recurrent headache have been reported as frequent. Hemiparesis, opisthotonos, temperature instability, apnea and abnormalities of muscular tone have also been described. Cranial nerve abnormalities and sensorineural hearing loss are rare features.[78] Unilateral brain lesions reported had cerebral arteriopathy and cutaneous hemangioma on the ipsilateral side.[79]

Segmental facial hemangiomas are the hallmark of this syndrome.[76] At birth, hemangiomas are subtle or non-existing, commonly becoming more obvious within the first days to weeks of life. Hemangiomas associated to PHACE syndrome have usually a diameter superior to 5 cm, with a characteristic aspect and location. The term “segmental” hemangioma is used, because these hemangiomas affect a territory, instead of arising from a single focal point. These hemangiomas can present as solitary lesions, confluent plaques or small individual papules clustered in a patterned distribution. In newborns, they can also present with a telangiectatic appearance or as a slightly erythematous patch.[78]

Frontotemporal location of hemangiomas is the most predictive of cerebrovascular and ocular anomalies, while when located in the mandible, chin, and lower lip (the beard location), hemangioma seems to be related with ventral development defects and cardiovascular anomalies. Reports of infants with PHACE syndrome characteristics without the classical hemangiomas are rare.[78] Large hemangiomas in patients with PHACE features can also be located on the posterior scalp, upper chest, upper proximal extremity, or can even be intraorbital. Small hemangiomas may be seen in the head. Although rare, intracranial hemangiomas can be seen with higher frequency in PHACE syndrome. They can be located in the auditory canal or cavernous sinus ipsilateral to other CNS anomalies and to the skin hemangiomas.[79]

These segmental hemangiomas not only contribute to patients’ morbidity, but can also be life-threatening, as it occurs, for instance, in airway hemangioma.[76] Bilateral involvement of the beard location of hemangioma is associated with airway hemangiomas.[80] Facial hemangioma can lead to some complications, such as ulcerations with bleeding, amblyopia if blocking the visual axis, and feeding difficulties in case of perioral hemangioma.[76] Dysphagia can be secondary to the disease location – lip, oral cavity, and pharynx – or oral motor coordination.[79]

The most common extracutaneous anomaly in PHACE syndrome is cerebrovascular involvement.[76,78] There is a report with a prevalence of 77.4% of cerebrovascular anomalies in a cohort of 115 PHACE patients.[76] Arterial lesions are far more common than venous and cerebral sinus anomalies.[78]

Cerebrovascular abnormalities can include dysplasia; narrowing, which includes developmental hypoplasia or agenesis and acquired stenosis or occlusion; aberrant origin or course; and persistence of embryonic anastomosis.[76,78] Arterial dysplasia is probably the most common arterial anomaly. Severe forms of arterial dysplasia observed in this syndrome generate such high degrees of arterial tortuosity that make this almost a distinguish feature, only seen in some other rare diseases, such as MD. Aneurysms may also be present in some patients. Variants within the circle of Willis can also be more frequent in these children, although they are not part of the diagnostic criteria, due to the lack of diagnostic specificity.[78]

Typically, the most affected arteries are both intracranial and extracranial ICA, MCA, ACA, PCA, the basilar artery and the vertebral arteries. Arterial abnormalities are generally ipsilateral to the cutaneous hemangioma or bilateral.[78]

The most frequent cardiac abnormality found in PHACE syndrome is coarctation of the aorta. As it is a life-threatening condition, its recognition is critical. In PHACE syndrome, it can be associated with long-segment hypoplasia/interruption of the transverse arch and dilation and aneurysm formation in adjacent arch segments. Arch abnormalities are often associated with anomalies in brachiocephalic vessels and aortic arch sidedness (right or double aortic arch). Unlike non-syndromic aortic coarctation, this related with PHACE syndrome is not commonly associated with mitral or aortic valve abnormalities.[78]

Another cardiac abnormality with a higher incidence in this syndrome than in general population is ventricular septal defect. Patent *foramen ovale* is also commonly reported, although it is a normal finding in about 25% of the general population, so it is not considered as a diagnostic feature of PHACE syndrome.[78]

Anomalies in cerebral and cardiac arteries lead to an increased risk of stroke. Actually, some risk factors for AIS have been identified in PHACE syndrome patients, such as aplasia, hypoplasia or occlusion of at least 1 cerebral artery, additional aortic arch anomalies, thromboembolism related to cardiac and supra-aortic arterial lesions, and treatment with corticosteroids.[76,79] In a review of 22 published cases of stroke in PHACE syndrome patients, all patients with stroke had an AIS in the distribution of at least 1 narrow or nonvisualized major cerebral artery and 79% had 2 or more abnormal arteries. Risk for AIS in patients with PHACE syndrome has been stratified in 3 levels – low, intermediate or high –, according to the existing arterial abnormalities.[79]

Ocular abnormalities are not very common in this syndrome, but specific posterior segmental anomalies, when associated with an ipsilateral segmental hemangioma, are very

specific. The most commonly described are microphthalmia, optic nerve hypoplasia, persistent fetal vasculature, and morning glory disc anomalies.[78]

Ventral development defects, such as sternal clefting and/or supraumbilical abdominal raphe, have been reported associated with this syndrome.[78] Endocrine anomalies involving the pituitary and/or thyroid glands can also be related to this condition in patients with midline defects. Endocrinological disorders in these patients include hypopituitarism, growth hormone deficiency, hypogonadotropic hypogonadism, central adrenal insufficiency, and central hypothyroidism. Moreover, thyroid dysgenesis may be present at birth. Growth hormone deficiency is the most common hypothalamic-pituitary disfunction disorder in these patients, resulting in a deterioration of growth in early life.[81]

Headache is more frequent and severe and may present earlier in children with PHACE syndrome.[79] Nearly 55% of patients of a large PHACE syndrome cohort suffered from headache. If a child presents with new headache, it is important to do a thorough evaluation for secondary causes of headache, such as vasculopathy and AIS.[79] The clinical characteristics of the headache may vary. Many patients reported concomitant migraine symptoms such as nausea, vomiting, photophobia, and phonophobia. Auras or premonitory symptoms were also reported in a large PHACE syndrome cohort in 26.5% of patients, described as an “ill feeling” or a visual disturbance preceding headache.[82]

Some dental abnormalities, such as dental enamel hypoplasia and absent dental roots, have also been described in PHACE syndrome patients.[79]

Segmental hemangiomas located on the lower body can be related with structural birth defects, reported as LUMBAR syndrome: lower body hemangiomas (L); urogenital anomalies (U); myelopathy (M); bone deformities (B); anorectal malformations/arterial anomalies (A); renal anomalies (R). There is an important overlap between characteristics of PHACE and LUMBAR syndromes, hypothesizing that these syndromes may be regional variations of the same syndrome.[77] Association of PHACE syndrome to coagulopathies has been discarded.[76]

6.5.3. Etiology and Pathophysiology

To determine if there are prenatal risk factors for PHACE syndrome, a study was developed. It concluded that the rates of preeclampsia and placenta previa during the gestation of PHACE syndrome patients were significantly higher than in general population.

Also, known or suspected miscarriage rates were significantly higher than in the general population.[77]

Unilateral cerebellar hypoplasia (UCH) is frequently associated with anomalies of the ipsilateral ICA or persistent embryonic carotid-vertebrobasilar connections and there is a well stablished association between prenatal hypoxic-ischemic insult and UCH. These two associations suggest that abnormal arterial development in this syndrome may cause hypoxia in utero, leading to an underdeveloped cerebellum.[83]

This is a sporadic condition with no reports of recurrence in families. Moreover, only a small number of adult women affected by this disease have had children and there are no reports of PHACE syndrome phenotype in their children.[77]

Various studies have been developed to understand the reason for female preponderance of this condition. The role of skewed X-inactivation has been discarded. Another hypothesis was that this syndrome could be X-linked with male lethality. Though, it was concluded that this explanation is unlikely, as there are no significant differences in phenotypic features between males and females. It is worth mentioning that the incidence of sporadic infantile hemangioma is also higher in females, with a female-to-male ratio of 3.1:1. Explanation of female preponderance in both PHACE syndrome and sporadic infantile hemangioma remains unknown.[77] Some authors have also hypothesized that a developmental error between the 6th and 8th week of gestation, affecting the neural crest, could be responsible for PHACE syndrome's features.[84]

CNV analysis as also been performed. Large, rare copy gains and copy losses were identified in different locus, but no shared deleterious CNVs among affected individuals were detected. As most genes implicated in vascular and skin anomaly syndromes were oncogenes and tumor suppressor genes, it has also been hypothesized that these genes can be responsible for PHACE syndrome pathogenesis. Further studies are necessary.[77] A specific deletion on 7q33 has been identified in two out of 16 patients with PHACE syndrome in a 2012 study. Although these deletions are probably not the single cause of PHACE syndrome, they may provide genetic susceptibility in combination with other inherited or *de novo* CNVs.[85]

There are some possible mechanisms to explain stroke in patients with PHACE syndrome: artery-to-artery embolisms; ischemia from diminished blood flow; cardioembolism.[86] Headache in these patients may result from the anomalies of the circle of Willis and from the progressive cerebrovascular changes, such as MMS. Patent *foramen*

ovale can also trigger migraine by allowing vasoactive substances to bypass pulmonary circulation and reach the brain. It is also important to consider that headache prevalence in general children population increases with age.[82]

6.5.4. PHACE syndrome and Moyamoya

Several patients with PHACE syndrome with development of a network of collaterals to compensate for stenosis or occlusion of a major cerebral artery, just like Moyamoya, have been reported. However, only about 7% of PHACE patients presented with MMS.[77] All reported PHACE patients with MMS have associated congenital anomalies of cervical and/or cerebral arteries, but not all patients with congenital arterial anomalies develop MMS. Nevertheless, identified PHACE patients are still young and MMS is a progressive disorder, so its incidence in PHACE syndrome may be underestimated.[87]

Two compound heterozygous *RNF213* gene variants have been reported in association with MMS in a PHACE syndrome patient. Further studies are needed to better understand the importance and frequency of *RNF213* gene in PHACE syndrome.[87] MMS was bilateral in the majority of cases reviewed in a 2017 study.[75]

6.5.5. Diagnosis

Diagnostic criteria categorize patients into definitive or possible PHACE syndrome.[78] Diagnosis is reached in the presence of infantile hemangiomas in the face or scalp with more than 5 cm in diameter and 1 major diagnostic criterion; or in the presence of large segmental infantile hemangiomas of the neck, upper trunk, or trunk and proximal upper extremity in association with 2 major criteria. Possible PHACE diagnosis is considered when there is a hemangioma of the head with more than 5 cm in diameter and 1 minor criterion; or hemangioma of the neck, upper trunk or trunk and proximal upper extremity in association with 1 major or 2 minor criteria; or no hemangioma but 2 major criteria present. [79] This data and major and minor criteria are summarized in Table 3.

Table 3. Diagnostic criteria for PHACE Syndrome.[79]

Affected organ systems	Major criteria	Minor criteria
Arterial system	Anomaly of major cerebral or cervical arteries (ICA, MCA, ACA, PCA or vertebrobasilar system) Dysplasia (includes kinking, looping, tortuosity, and/or dolichoectasia) of the large cerebral arteries Arterial stenosis or occlusion with or without Moyamoya collaterals Absence or moderate-severe hypoplasia of the large cerebral and cervical arteries Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch. Persistent carotid- vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic and/or trigeminal arteries)	Aneurysm of any of the cerebral arteries
Structural brain	Posterior fossa brain anomalies Dandy-Walker complex Other hypoplasia/dysplasia of the mid and/or hind brain	Midline brain anomalies Malformation of cortical development
Cardiovascular	Aortic arch anomalies Coarctation of the aorta Dysplasia Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch/double aortic arch Systemic venous anomalies
Ocular	Posterior segment abnormalities Persistent hyperplastic primary vitreous Persistent fetal vasculature Retinal vascular anomalies Morning glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma	Anterior segment abnormalities Microphthalmia Sclerocornea Coloboma Cataracts
Ventral/midline	Anomaly of the midline chest and abdomen - Sternal defect - Sternal pit - Sternal cleft - Supraumbilical raphe	Ectopic thyroid hypopituitarism Midline sternal papule/hamartoma
Definite PHACE syndrome		
Hemangioma >5 cm in diameter of the head including scalp PLUS 1 major criterion or 2 minor criteria Or Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 2 major criteria		

Possible PHACE syndrome
Hemangioma > 5 cm in diameter of the head including scalp PLUS 1 minor criterion
Or
Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 1 major or 2 minor criteria
Or
No hemangioma PLUS 2 major criteria

Abbreviations: ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery

Infants with hemangiomas suggesting PHACE syndrome should undergo a thorough evaluation that must include MRI and MRA brain imaging, imaging of the cardiac vessels and an ophthalmologic examination.[78] In patients with respiratory symptoms or extensive facial hemangioma in the beard location, evaluation with laryngoscopy and bronchoscopy should be performed in order to exclude airway hemangioma.[76]

Some cerebrovascular abnormalities may be identified in routine MRI. Nevertheless, an MRA is needed to identify and characterize more extensively and with certainty these anomalies.[78] Serial neuroimaging, specifically with brain MRI and MRA, is recommended by some clinicians and researchers, when cerebrovascular abnormalities are detected.[74]

Children considered at-risk for PHACE syndrome should undergo a screening echocardiogram. If abnormalities are found, a cardiac MRI/MRA is recommended, to understand the arch and brachiocephalic anatomy thoroughly. A screening MRI with and without gadolinium and MRA of the head, neck and aortic arch should be executed.[79] Around 90% of reported patients with PHACE syndrome have anomalies – congenital malformations or arteriopathy – on brain MRI or MRA.[88]

Clinical screening of aortic coarctation by blood pressure difference between upper limbs and lower limbs cannot be considered reliable on these patients, because of the aberrant origin of the subclavian artery causing arch obstruction above the level of origin of the major arteries for the limbs.[78] If midline defects are present, a radiographic study should be performed to assess chest wall development.[74] Growth should be regularly monitored, as well as thyroid function testing.[81] Endocrinology evaluation may be adequate, particularly for patients with abnormal pituitary structure or empty sella on MRI or with extensive hemangiomatosis.[74]

6.5.6. Treatment

If Dandy-Walker malformation is detected in a brain MRI, these children must be evaluated by a neurosurgeon. Structural brain lesions must be assessed by pediatric neurology or neurosurgery.[88]

Propranolol, a ß-blocker, as proven to be effective in the treatment of facial hemangioma.[76] This drug is also used in the treatment of airway hemangiomas and has more effectiveness and less side effects than other therapeutics modalities, such as corticosteroids and CO_2 lasers. Propranolol side effects are hypotension, bradycardia, hypoglycemia and bronchospasm.[80] There has not been found a correlation between propranolol use and stroke in patients with PHACE syndrome.[89] Systemic corticosteroids are only recommended in life-threatening or refractory situations, such as respiratory distress in airway hemangioma, and for 14 days maximum.[76]

About 37% of patients with arch anomalies will need surgical intervention and extensive arch reconstruction is frequently necessary. Patients with high or intermediate risk of stroke should avoid contact sports and activities that involve extreme neck positions.[79] In asymptomatic high-risk patients for stroke, acetylsalicylic acid (4-5 mg/kg) should be considered as prophylaxis and it has been used with successful results following acute stroke in a small case series of infants suffering from this syndrome.[76]

Recombinant growth hormone therapy can be used in growth-hormone deficiency, increasing the linear growth rate.[81] Existing arterial abnormalities in this syndrome are a relative contraindication for vasoconstrictive headache treatment, including triptans, dihydroergotamine, and ergotamine tartrate.[79]

Indirect revascularization procedures have been performed with success in PHACE patients with MMS.[74] It is important to monitor these children for language delay and assess their need of speech therapy.[88]

6.5.7. Prognosis and Evolution

If marked vessel tortuosity and turbulent blood flow are present, patients with intermediate risk of stroke may have increased risk for thrombus formation or aneurysm in adulthood.[79] Also, PHACE syndrome patients may be at risk of stroke in childhood.[84]

Vascular anomalies influence long-term outcomes of PHACE syndrome patients as up to 50% of patients become symptomatic due to the progressive intracranial arteriopathy. In a 2017 study, all patients with MMS and PHACE syndrome surgically treated had no new ischemic infarcts in a mean follow-up period of 13.6 months (range 5-25 months). Also, neurologic symptoms improved in 6 of the 9 operated cases, while the other 3 patients remained stable at last follow-up.[75] Some children presenting with headache may have diminished participation in school and social activities and a negative impact on quality of life. This can cause substantial headache-related disability.[82] Neurological and cognitive impairments are considered the greatest source of potential morbidity.[88]

7. CONCLUSION

Genetic arteriopathies can affect only cerebral vessels, like in MMD, or be part of a syndrome with multi-organ disease. They often lead to events or complications with great impact not only in individual prognosis, but also at a socioeconomic level. There are already some treatment measures for these conditions, such as revascularization procedures, and preventive measures, such as antiplatelet agents to prevent stroke, but further investigation is necessary in order to develop targeted strategies and provide better outcomes for these children.

Most of these patients undergo surgical procedures during their childhood. Peri-operative routines require a multidisciplinary approach, as all their comorbidities need to be correctly assessed to reduce the surgical risk and to provide the best possible outcome. This multidisciplinary approach is also very important in the follow-up process.

Being rare conditions makes them harder to be identified and delayed diagnosis can lead to serious complications, some of them life-threatening, and to worse prognosis. As they have long-term implications both to patients and their caregivers, their identification is crucial to implement therapeutic measures with impact on prognosis and quality of life. Therefore, it is of extreme relevance to elaborate about these conditions and summarize the existing knowledge. Actually, that is an important measure to generate further research in such needed field.

8. ACKNOWLEDGEMENTS

I would like to thank my family for always supporting and encouraging my dreams.

I would also like to thank my friends for the long journey we made together, from Azores to Coimbra, both through dark and amazing moments

I would like to thank Miguel for his infinite patience and support through all this process.

Last but not least, I would like to thank Dr. Filipe Palavra and Doctor Ricardo Faustino for their contribution.

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