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CASE REPORT

Moyamoya angiopathy in PHACE syndrome not associated with RNF213 variants

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Abstract

Moyamoya angiopathy is a rare vasculopathy with stenosis and/or occlusion of bilateral intracranial parts of internal carotid arteries and/or proximal parts of middle and anterior cerebral arteries. PHACE syndrome is characterized by large segmental hemangiomas in the cervical-facial region. Both conditions are known to be associated in rare cases. Recently, it was discussed in the literature that RNF213 variants could be etiologically involved in this association. Here, we describe a childhood case with this rare co-occurrence in which we did not identify any rare RNF213 variant. The clinical and genetic backgrounds are discussed.

Keywords PHACE · Moyamoya angiopathy · Rare RNF 213 variants

Introduction

PHACE syndrome (acronym for posterior fossa anomalies, hemangioma, arterial abnormalities, cardiac abnormalities, eye anomalies) is a very rare neurocutaneous disease of unclear etiology characterized by large segmental hemangiomas in the cervical-facial region combined with other developmental defects [1, 2]. Moyamoya angiopathy (MMA) is a cerebral angiopathy characterized by steno-occlusive lesions involving the terminal part of the internal carotid arteries (ICA) and/or the proximal parts of the middle and anterior cerebral arteries, and may lead to hemodynamic ischemic strokes as well as intracranial hemorrhages. The term moyamoya disease (MMD) refers to the isolated form of the angiopathy; the term moyamoya syndromes (MMS) is used when MMA is associated with other conditions, including genetic conditions such as type 1 neurofibromatosis or down syndrome. PHACE syndrome, in which some patients may develop a MMA, belongs to MMS [3]. The etiology of PHACE syndrome and the reason for its association with MMA are unknown. By contrast, genetic determinants of MMA has been intensively studied [4, 5]. In Asia, the RNF213 founder variant p.R4810.K is closely associated with MMA development [5–7]. In Caucasians patients, this founder variant is totally absent [8]. However, also the RNF213 gene seems to play an important role in Caucasian MMA patients as rare variants distinct to p.R4810K were described to be associated with MMA [9], especially when located in a C-terminal hotspot encompassing the RING finger domain of the protein [10–12]. Recent data suggests that RNF213 variants also increase the risk to develop MMA in some syndromic conditions such as type 1 neurofibromatosis [13, 14]. Recently, Schilter et al. identified a compound heterozygous variant in RNF213 (p.W4677L and p.Q469H) in a child showing association of PHACE and MMA [15]. The parents of this patient were from Caucasian and African-American origin. The p.W4677L variant had already been identified in a Caucasian MMA family without PHACE syndrome [11]. Herein, we present a patient with MMA in which retrospective diagnosis of PHACE syndrome

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was established, and who is not mutated in RNF213 gene. Genetic data are provided and discussed.

Clinical presentation

A 28-year-old female patient was admitted to our neurological clinic in August 2017. The patient had already been suspected suffering from MMA with 3 years, since she had experienced two ischemic strokes at the age of 1 and 3 years. Her neurological status showed a right accentuated spastic tetraparesis. Her family history was unremarkable. Her family background was Caucasian European.

She reported that she had a port-wine stain on the right side of her face until the age of six, which spontaneously regressed during school age (Fig. 1). Furthermore, she suffered from right-sided amaurosis since central retinal artery occlusion. At the age of 8 years, the patient experienced a 2-min episode of weakness of the right hand. At the age of 17 years, she had a transient prickling of the right arm for about 5–10 min. These events were diagnosed as focal seizures and treated with an anticonvulsive medication.

The cerebral MRI examination (Fig. 2a) showed—unchanged to earlier examinations—gliotic defects on the right hemisphere with e vacuo-extension of the lateral ventricle as well as hemodynamic left hemispheric defects. MR perfusion showed a nearly normal brain perfusion (Fig. 2b). The conventional angiography showed a bottle-neck-like occlusion of the internal carotid artery on the right side, meanwhile the brain supply was mainly provided by the collaterals of the external carotid artery (stage IV according to Suzuki). The left distal internal carotid artery as well as the main trunks of the MCA and ACA was occluded, and extensive ethmoidal and leptomeningeal collaterals were depicted in MR (Fig. 2c) and conventional angiography (stage IV according to Suzuki).

With sufficiently stable hemodynamic conditions due to the natural collateral circuits and stable clinical findings, we did not see any indication for a revascularizing bypass surgery and recommended further platelet antiaggregation therapy.

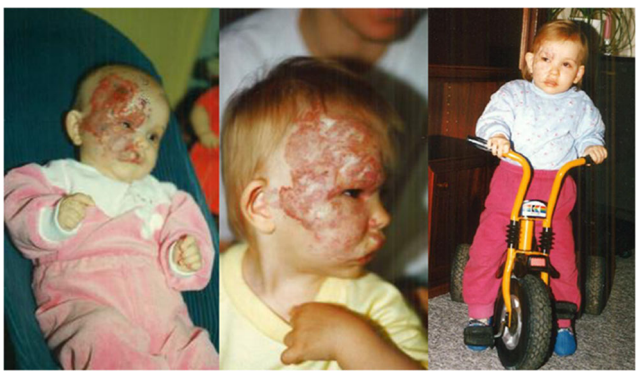

Fig. 1 Pictures of the patient in childhood with typical port-wine stain on the right side of the face with spontaneously regression with school age

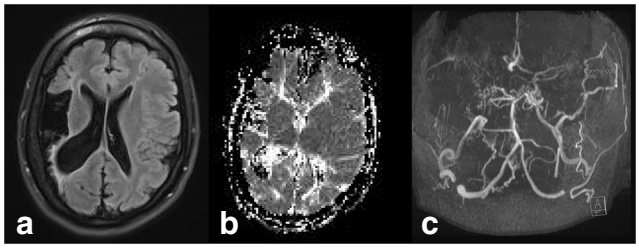

Fig. 2 **a** Flair MRI imaging with gliosis and postischemic atrophy, **b** MR perfusion imaging with relatively good hemodynamic situation (gray), **c** MR angiography of the same patient with typical bilateral moyamoya phenomenon

Methods

The study was approved by the Ethics Committee of the University of Duisburg-Essen. The participant gave her written informed consent in order to publish the results and use her photos for publication. In order to investigate the putative genetic causes of MMA in this patient, a targeted next-generation sequencing (NGS) of a panel of 12 genes was performed. This panel included RNF213 (NM_001256071.1) and 11 genes known to be involved in known Mendelian MMS: PTPN11 (NM_002834.3), SHOC2 (NM_001269039.1), NF1 (NM_000267.3), JAG1 (NM_000214.2), CBL (NM_005188.3), ACTA2 (NM_001141945.1), GUCY1A3 (NM_000856.5), BRCC3/MTCP1 (NM_001018055.2 and NM_001018025.3), SAMHD1 (NM_015474.3), PCNT (NM_006031.5), SMARCAL1 (001127207.1). This list of 11 genes involved in Mendelian MMS has been drafted based on previously published data. DNA was extracted from peripheral-blood leukocytes according standard procedures, using the Wizard genomic purification kit. DNA libraries were prepared using the SureSelect QXT sample preparation kit (Agilent technologies, Santa Clara, CA, USA). The libraries were prepared according to the manufacturer's instructions and sequenced on an Illumina MiSeq instrument with 2 × 150-pb paired-end reads, according to standard Illumina protocols. SeqNext 4.4 software (JSI Medical Systems, Germany) was used for mapping and analysis of data. All regions of interest were analyzed at coverage of at least 50×. Meanwhile, VariantStudio™ 3.0 software (Illumina, San Diego, CA, USA) was used to strengthen bioinformatics analysis. Coding variants in RNF213 with an allele frequency > 1% were excluded. A specific search for RNF213 variants c.1407G>T (p.Q469H) and c.14030G>T (p.W4677L) identified by Schilter et al. [15] was performed. For the 11 other analyzed genes, coding variants with an allele frequency above 1‰ were excluded.

Table 1 Review of all reported cases adapted to Tortora et al. [18]

No. (sex)	Age of onset	Age of diagnosis	Neurological symptoms	Stroke	Vascular impairments	Moyamoya phenomenon	Hemangioma location	Posterior Fossa anomalies	Cardiovascular anomalies	Eye anomalies	Reference
1 (N-A)	4 months	18 months	Motor delay, hemiparesis left	Yes	MCA, ACA, and PCA left occlusion, MCA right stenosis, ACA right occlusion	Bilateral	Cervicofacial bilateral	No	No	No	Burrows et al. (1998)
2 (N-A)	10 months	10 months	Seizures, hemiparesis left	Yes	ICA and PCA bilateral occlusion, ICA right aneurysm, small left ICA	Bilateral	Orbital, periorbital right	No	No	No	Burrows et al. (1998)
3 (N-A)	1 month	16 months	Seizures	Yes	Absent supraclinoid ICA left and PCA right, ICA right occlusion, aberrant MCA origin left, ICA right aneurysm	Bilateral	Orbitofacial right	Cerebellar hypoplasia right, horner syndrome, posterior fossa anomaly	Absent aortic arch right, aberrant left subclavian artery	No	Burrows et al. (1998)
4 (♀)	1 month	48 months	Headache, neurocognitive deficit	No	ICA bifurcation right occlusion, ICA left narrowing, VA bilateral hypoplasia	Bilateral	Maxilla, eye	No	Aortic coarctation	No	Bhattacharya et al. (2004)
5 (♀)	6 months	6 months	Motor deficits, chorea, headaches	No	ICA bifurcation right occlusion, supraclinoid ICA left stenosis, ACA left occlusion, distal BA occlusion	Bilateral	Eyelid, eye	No	No	No	Bhattacharya et al. (2004)
6 (♀)	14 years	14 years	Headaches	No	Supraclinoid ICA left stenosis, dysplastic ICA right, aneurysm MCA formation, PICA left hypoplastic	Unilateral left	No	No	No	No	Bhattacharya et al. (2004)
7 (♂)	14 years	14 years	Aphasia, hemiplegia right	Yes	Supraclinoid ICA, MCA and ACA left occlusion, MCA and PCA right aneurysms	Unilateral left	No	No	No	No	Bhattacharya et al. (2004)
8 (♂)	4 months	4 months	Seizures, hemiparesis right	Yes	ICA, ACA, and MCA left narrowing	Unilateral left	Mandibular cheek left	No	Patent foramen ovale	Eye deviation, nystagmus	Drolet et al. (2006)
9 (♀)	1 month	12 months	Hemiparesis left	Yes	Cervical ICA narrowing bilateral, intracranial ICA and ACA right stenosis, PCA left tortuosity	Bilateral	Face right, periorbital and orbits bilateral, intracranial	No	No	Ptosis bilateral	Drolet et al. (2006)
10 (♀)	1 month	5 months	Left hemiparesis, seizure	Yes	ICA bilateral stenosis, meningeal bilateral collateralization	Bilateral	Temporal region and eyelid left	No	Aortic isthmus hypoplasia	No	Heyer et al. (2006)
11 (♀)	7 months	4 years	Irritability, lethargy, headaches with	Yes	Absent ICA right, absent VA right, abnormal origin VA left and subclavian artery right, ICA left stenosis, PCA bilateral stenosis, BA tortuosity	Bilateral	Periorbital and temporal region, orbit left	Cerebellar hypoplasia left	No	Exotropia left	Heyer et al. (2008)

Table 1 (continued)

No. (sex)	Age of onset	Age of diagnosis	Neurological symptoms	Stroke	Vascular impairments	Moyamoya phenomenon	Hemangioma location	Posterior Fossa anomalies	Cardiovascular anomalies	Eye anomalies	Reference
			associated vomiting								
12 (♂)	11 months	17 months	Hemiparesis right, focal seizure right	Yes	Absent VA and ICA right, VA and ICA left tortuosity, persistent left proatlantal and trigeminal arteries, enlargement of both ECA	Bilateral	Mid-thoracic region, preauricular left, superior cervical areas and nose	No	Congenital cardiopathy, aortic coarctation	No	Pascual-Castroviejo et al. (2009)
13 (♀)	1 month	31 months	Hemiparesis right, facial focal seizures	Yes	Terminal ICA bilateral stenosis, ICA, BA distal, and PCA right occlusion	Bilateral	Side of the face right, retroauricular area, neck, chest, and posterior palate	No	Trace tricuspid regurgitation	Strabismus and ambly-opia of the right eye	Sathiskumar et al. (2013)
14 (♀)	5 months	18 months	Hemiparesis left, seizure	Yes	ICA left occlusion, supraclinoid ICA right stenosis, PCoA left stenosis	Bilateral	Parotid glands bilateral and maxillar and mandibular area right	No	Tricuspid regurgitation, ventricular septal and small atrial septal defect	No	Jack et al. (2016)
15 (♀)	5 years	5 years	Vomiting, headaches	No	ICA tortuosity bilateral, MCA left narrowing, PCA left hypoplasia	Bilateral	Sacral back extending to the right posterior thigh and ankle	No	No	Posterior staphylo-ma left	Schilter et al. (2017)
16 (♀)	18 months	10 years	Headaches, mild developmen-tal delay	Yes	Supraclinoid ICA right stenosis, ACA bilateral stenosis	Bilateral	Side of the face left, palatal mucosa, intracranial	Cerebellar hypoplasia left	Aortic isthmus hypoplasia	Morning glory disc anoma-lies bilateral	Tortora et al. (2017)
17 (♀)	12 months	12 months	Hemiparesis left, seizures, headaches, pyramidal signs right	Yes	ICA bilateral narrowing, MCA left stenosis	Bilateral	No	Hypoplasia midbrain and pons left	No	No	Tortora et al. (2017)
18 (♀)	3 months	5 years	Headaches	No	Supraclinoid ICA left stenosis, ACA left hypoplasia, VA stenosis, persistent primitive trigeminal artery	Bilateral	Orbital region right, intraorbital and intracranial	No	No	Morning glory disc anomaly right	Tortora et al. (2017)
19 (♀)	1 month	30 months	Seizures	Yes	ICA left hypoplasia, MCA left aneurysm, and tortuosity	Unilateral left	NA	NA	NA	NA	Tortora et al. (2017)
20 (♂)	NA	1 month	Asymptomatic	Yes		Bilateral	NA	NA	NA	NA	Tortora et al. (2017)

Table 1 (continued)

No. (sex)	Age of onset	Age of diagnosis	Neurological symptoms	Stroke	Vascular impairments	Moyamoya phenomenon	Hemangioma location	Posterior Fossa anomalies	Cardiovascular anomalies	Eye anomalies	Reference
					Absent ICA left, ICA right, and MCA left stenosis, MCA right narrowing, BA aneurysm						
22 (♀)	1 month	10 months	Seizure	No	Supraclinoid ICA bilateral stenosis, BA aneurysm, MCA left tortuosity	Bilateral	NA	NA	NA	NA	Tortora et al. (2017)
23–31 (♀)	NA	NA	Seizures (3 out of 8); Headaches (4 out of 8)	Yes (3 out of 8)	NA; narrowing petrous carotids (8 out of 8); basilar artery anomalies, stenosis (5 out of 8)	Bilateral (5 out of 8), Unilateral (3 out of 8) 1 left, 2 right	NA	NA	NA	NA	Jernigan et al. (2019)
32 (♀)	12 months	3 years	Seizures, tetraparesis	Yes	Supraclinoid ICA bilateral occlusion	Bilateral	Port-wine stain right face	No	No	Amaurosis right	Present publication

NA, not available; *ICA*, internal carotid artery; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *BA*, basilar artery; *VA*, vertebral artery; *PCoA*, posterior communicant artery; *PICA*, posterior inferior cerebellar artery; *ECA*, external carotid artery

Results

The genetic analysis did not reveal any candidate variant in the RNF213 gene, neither the two variants formerly described by Schilter et al. [15], nor rare variant in the C-terminal Caucasian hotspot [10]. As expected, the Asian p.R4810K variant was also absent.

In addition, the genetic screening for the 11 MMS genes did not identify any deleterious mutations.

Discussion

PHACE syndrome is a very rare disease with unknown incidence and prevalence [16]. It occurs sporadically and preferably in a ratio of 4.2:1 in the female sex [2]. The most common manifestation characteristic for PHACE syndrome is early childhood hemangiomas on the face. The larger the hemangioma are or the more segments are affected, the higher the risk of PHACE syndrome [17].

Congenital cerebral vascular malformations are the most frequent extracutaneous manifestation of the syndrome. In addition to the persistence of embryonal arteries, this also includes agenesis of vertebral or carotid arteries. In particular, the latter two can become progressively stenotic and can result in MMA or moyamoya-like syndrome [18]. To date, only a few patients showing a co-occurrence of PHACE and MMA have been reported in the literature [13–15, 18–25] (Table 1). Malformations of the posterior cranial cavity, such as cerebellar hypoplasia, arachnoid cysts, cortical dysgenesis, or Dandy-Walker malformations, which typically occur ipsilaterally to the cerebrovascular changes, represent other CNS manifestations of the disease [26].

Expert consensus-based diagnostic criteria for the PHACE syndrome were published 2016, after which the diagnosis is made in the presence of a facial hemangioma with a diameter of > 5 cm plus one major or two minor criteria [16, 17, 27]. Retrospectively, the diagnosis of PHACE syndrome could be made in our case [16]. In this study, the diagnosis of the patient was based on the facial port-wine stain during childhood and occlusion of internal carotids (major criteria) [16].

The causes triggering MMA in PHACE are still not understood. To our knowledge, Schilter's [15] study and our study are the only two studies to report genetic data about patients showing a co-occurrence of PHACE and MMA.

Schilter et al. recently identified in a young patient showing co-occurrence of MMA and PHACE a compound heterozygous mutation in the RNF213 MMA susceptibility gene [15].

In contrast to the recently reported case from Schilter et al. [15], our case did not carry any candidate variant in the RNF213 gene.

Guey et al. showed in 2017 that rare RNF213 variants are found in about 15% of healthy controls [10]. With such a

frequency in the general population, identification of RNF213 variants in a unique PHACE patient with MMA could be coincidental. The absence of RNF213 candidate variant in the present case shows that MMA can occur in PHACE patients who are not RNF213 mutated. However, we cannot exclude that the presence of rare RNF213 variants in PHACE patients could increase their risk to develop MMA. Indeed, some studies showed that the risk to develop a MMA in some MMS such as type 1 neurofibromatosis was increased in the presence of RNF213 variants, in line with an oligogenic hypothesis [28, 29]. Additional larger studies are needed to solve this point.

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Compliance with ethical standards The study was approved by the Ethics Committee of the University of Duisburg-Essen. The participant gave her written informed consent in order to publish the results and use her photos for publication.

Conflict of interest The authors declare that they have no conflict of interest.

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