LATE DIAGNOSED PHACE SYNDROME BY ANEURYSMAL SUBARACHNOID HEMORRHAGE. CASE REPORT

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LATE DIAGNOSED PHACE SYNDROME BY ANEURYSMAL SUBARACHNOID HEMORRHAGE. CASE REPORT: PHACE syndrome is a neurocutaneous disorder coined in 1996, but the clear criteria of diagnostic were established in 2009. Even though the age of the diagnostic for the disease is during childhood, we present the case of a patient with PHACE syndrome with late diagnostic, at the age of 59-year-old by aneurysmal subarachnoid hemorrhage. The particularity of this case is represented by the paucity of the diagnostic criteria, respectively the presence of facial hemangioma and the dysplasia of the cerebral arteries at the level of Willis's circle, associated with two aneurysms: ruptured aneurysm of the right posterior communicating artery and unruptured aneurysm of junction P1-P2 of the left posterior cerebral artery. The aim of the article is to height line the importance of early diagnostic of PHACE syndrome and the prevention of complications. **Keywords:** PHACE, SYNDROME, CEREBRAL VASCULAR DYSPLASIA, SACCULAR ANEURYSM.

PHACE syndrome is a neurocutaneous syndrome coined in 1996 by the American professor of dermatology Frieden (1), and referred to the association: posterior fossa anomalies (P), hemangiomas of the face and scalp (H), arterial lesions (A), cardiovascular abnormalities (C) and eye's anomalies (E). When they are associated also supraumbilical raphe (S) or sternal clefting (S), it is called PHACES syndrome (2, 3).

PHACE syndrome appears mainly in women in 90% (1), suggesting that it could represent an X-chromosome-linked dominant condition with lethal potential in the male population. Anyway, familial cases have not been reported (4). Siegel *et al*. (5) made the first step in showing a potential genetic basis of PHACE syndrome, reporting the presence of a genomic copy number variation in patients having this syndrome. Till date, the pathogenesis of this syndrome is unknown (1).

CASE REPORT

We present the case of a patient aged 59, who was admitted at the Clinic of Neu-

rosurgery "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iasi, for the appearance of an intracranial hypertension syndrome dominated by severe headache. The examination underlined the presence of a facial hemangioma at the level of the left upper and lower eyelid, chin, the left cheek, respecting the alar nasal sulcus (figure 1). At the level of the left cheek, there was a scar in shape of heart ("heart" pseudo-sign) due to a free skin graft, which is mentioned in the personal medical history of the patient when she was 11 years old (fig.1). Computed tomography angiography (CTA) of the head and 3D reconstructions diagnosed a subarachnoid hemorrhage (SAH) (fig.2. A), cerebral vascular dysplasia (fig. 3), as well as a ruptured aneurysm of right posterior communicating artery (PCoA) (fig. 2. B and 3. A.), and a unruptured aneurysm of junction P1-P2 of the left posterior cerebral artery (PCA) (figure 3. B). The cerebral angiography confirmed the presence of the vascular dysplasia (figure 4.A), as well as the aneurysms (figure 4. B). It was not noticed the presence of other anomalies of the eyes or internal organs.

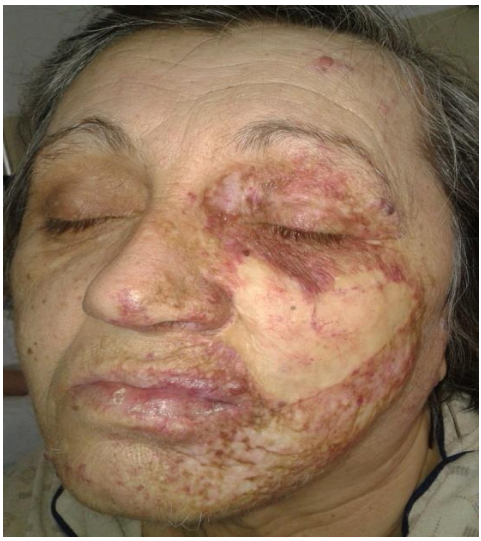

Fig. 1. Facial hemangioma in the distribution of segments 2 and 3. It is noticed the absence of cutaneous distribution of the trigeminal nerve, as do the "port wine stains" in Sturge Weber syndrome. It is also noticed the presence of a free skin graft with aspect of "heart".

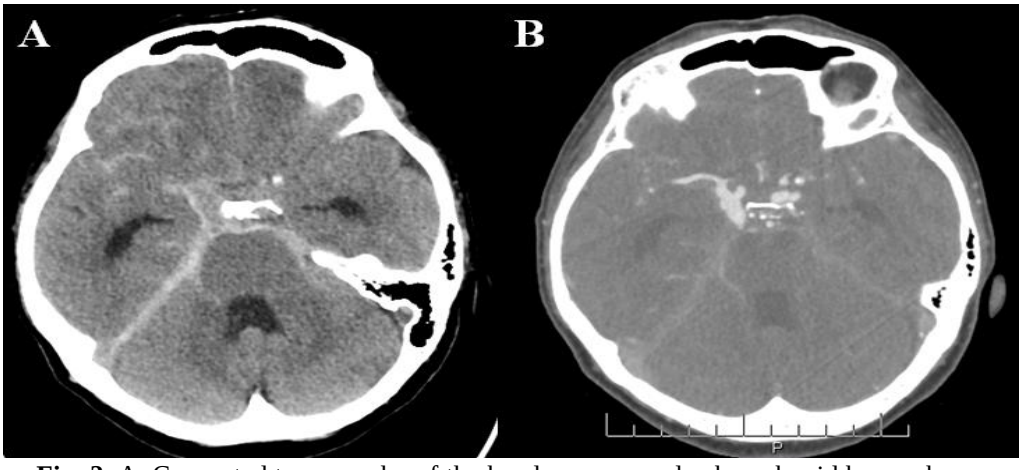

Fig. 2. A. Computed tomography of the head: aneurysmal subarachnoid hemorrhage; B. CTA: vascular dysplasia and right PCoA aneurysm.

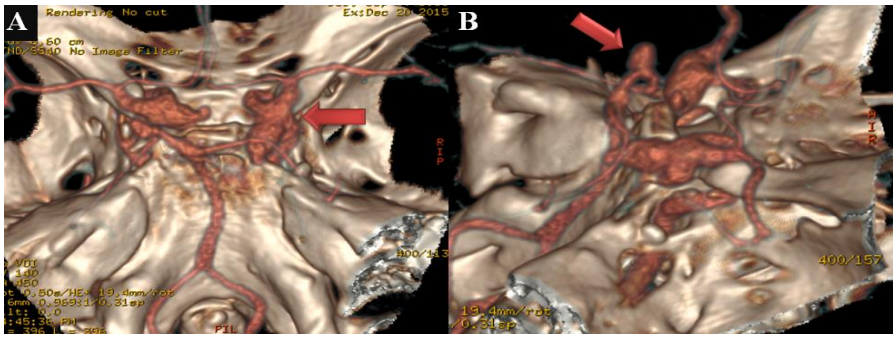

Fig. 3. A, B. CTA of the head with 3-dimensional reconstruction of the intracranial vessels showing dysplasia with right PCoA aneurysm (3. A, red arrow) and P1-P2 junction aneurysm (left PCA) (3. B, red arrow).

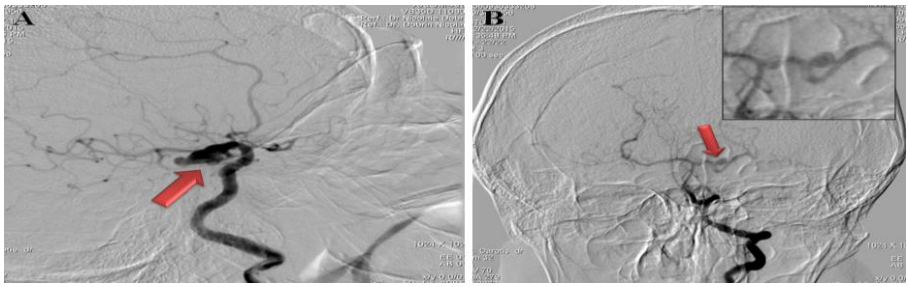

Fig. 4. Cerebral angiography: A. Lateral right view with vascular dysplasia (red arrow); B. Left vertebral artery view with P1-P2 junction aneurysm from left PCA (Dr. N.Dobrin's collection).

DISCUSSION

Criteria of diagnostic. Pascual-Castroviejo (6) was the one who proved for the first time the relationship between infantile hemangiomas and malformations of the cervical and cerebral arteries in a disease that he called "cutaneous hemangioma-vascular complex syndrome". In 1996, Frieden (1) suggest the acronym PHACES. The clear criteria of diagnostic for this syndrome were established in 2009 by the American Academy of Pediatrics, who classified them into two categories: 1. PHACE syndrome and 2. possible PHACE syndrome. Also, it has established the major and minor criteria that were determinate by following these organ systems: structural brain, cerebrovascular, cardiovascular, ventral or midline. Thus, definitive PHACES syndrome requires the presence of: facial hemangioma > 5 cm in diameter + 1 major criteria or 2 minor criteria; possible PHACES syndrome requires the presence of: facial hemangioma > 5 cm + 1 minor criteria, or hemangioma of the neck or upper torso + 1 major criteria or 2 minor criteria, or no hemangioma + 2 major criteria (7) (tab I). On considering these criteria, our patient fit into definitive PHACE syndrome, with the following valid criteria: facial hemangioma > 5 cm in diameter and dysplasia of large cerebral arteries, associated with two cerebral aneurysms.

The cerebrovascular abnormalities in PHACE syndrome. These anomalies are not only the most frequent extracutaneous man-

ifestation, but also the biggest potential source of morbidity, which can lead to the appearance of progressive vessel stenosis with acute ischemic stroke (4, 8). But the highest risk for the acute ischemic stroke is during infancy, between birth and 18 months, period that corresponds also to the cu hemangioma proliferative phase (4). This phase is followed by slow regression (9, 10). In the case of our patient, the cerebral vessels were not stenotic, and the onset was late, at the age of 59, by rupture of aneurysm of right PCoA. Even though within the syndrome isolated venous and cerebral sinus anomalies were reported, the arterial anomalies are the most frequent (7). They can be divided into four subcategories: 1: *dysplasia* (looping, kinking, ectasia or fusiform dilatation); 2: *narrowing* (agenesis, acquired stenosis or occlusion or developmental hypoplasia); 3: *aberrant course or origin of arteries* and 4: *persistence of embryonic anastomose*, and among then arterial dysplasia is the most frequent (7), present also in the case of our patient.

TABLE I.
Major and minor criteria for diagnostic of PHACE syndrome (4)

ORGAN SYSTEM	MAJOR CRITERIA	MINOR CRITERIA
Cerebrovascular	Anomaly of major cerebral arteries ▪ Dysplasia of the large cerebral arteries ▪ Arterial stenosis or occlusion with or without moyamoya collaterals ▪ Absence or moderate to severe hypoplasia of the large cerebral arteries ▪ Aberrant origin or course of the large cerebral arteries ▪ Persistent trigeminal artery ▪ Saccular aneurysms of any cerebral arteries	Persistent embryonic artery other than trigeminal artery ▪ Proatlantal intersegmental artery (types 1 and 2) ▪ Primitive hypoglossal artery ▪ Primitive otic artery
Structural brain	Posterior fossa anomaly ▪ Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia	Enhancing extra-axial lesion with features consistent with intracranial hemangioma ▪ Midline anomaly ▪ Neuronal migration disorder
Cardiovascular	Aortic arch anomaly ▪ Coarctation of aorta ▪ Aneurysm ▪ Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect ▪ Right aortic arch (double aortic arch)
Ocular	Posterior segment abnormality ▪ Persistent fetal vasculature (persistent hyperplastic primary vitreous) ▪ Retinal vascular anomalies ▪ Morning Glory disc anomaly ▪ Optic nerve hypoplasia ▪ Peripapillary staphyloma ▪ Coloboma	Anterior segment abnormality ▪ Sclerocornea ▪ Cataract ▪ Coloboma ▪ Microphthalmia
Ventral or midline	Sternal Defect ▪ Sternal cleft ▪ Supraumbilical raphe ▪ Sternal defects	Hypopituitarism ▪ Ectopic thyroid

The facial hemangioma in PHACE syndrome. The studies of facial hemangioma patterns have identified four primary facial segments: segment 1 (frontotemporal region), segment 2 (the maxillary region respecting the nasomedial sulcus), segment 3 (the mandible, chin and lower lip) and segment 4 (the medial frontal scalp, nasal bridge and philtrum) (11). In the case presented, the facial hemangioma was developed at the level of segments 2 and 3. Also, it seems that there is a relation within this syndrome, between the regional distribution of the facial hemangioma and the locations of arterial lesions (12).

Pathophysiology of PHACE syndrome. As for the physiopathology of the disease, based on the observations, Heyer *et al*. (12) have reached the conclusion that the initial vascular changes in PHACE start during the fifth week of embryogenesis, and infantile hemangioma and the cerebral vasculopathy of PHACE seem to be related temporally to an insult that appears in early embryogenesis. To understand the pathophysiological relation between facial hemangioma and cerebral arteries malformations, Burrows *et al.* (13) hypothesized the existence of vascular growth factors or other vascular modulators produced by the hemangioma itself, which would lead to the appearance of the cerebral arteriopathy. These factors that can be secreted during embryonic period of hemangioma formation or during the proliferative phase of hemangioma were well documented (12).

CONCLUSIONS

In the case of our patient, the presence of only a facial hemangioma and the absence of the other cardiovascular, cerebral, ocular or median line anomalies as well as sternal cleft, sternal defects or supraumbilical raphe, allowed the late diagnostic of the cerebral vasculopathy associated with aneurysm rupture. The early diagnostic of the PHACE syndrome is important in following and prevention of the possible complications.

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NEWS

ADVANCES IN ANTIBODY–DRUG CONJUGATES (ADCS) TECHNOLOGY

Antibody–drug conjugates (ADCs) are a potent class of anticancer therapeutics that comprise a high-affinity antibody (Ab) and cytotoxic payload coupled via a suitable linker for selective tumor cell killing. The first FDA-approved ADC was Mylotarg (gemtuzumab ozogamicin) but it was withdrawn from market, due to the acute adverse effects and morbidity in patients, attributed to acid-labile weak hydrazone linkers and nonspecific antigen expression in healthy cells. The limitations and failures of first-generation ADCs were eliminated in second-generation ADCs with the discovery of the breast cancer-targeting ADC, Kadcyla (ado-trastuzumab emtansine) and Adcetris (brentuximab vedotin) (for treating hematological cancer). Despite the improvement in cytotoxic payloads and the introduction of stable linkers, second-generation ADCs have significant limitations in terms of their heterogeneous DAR, resulting from stochastic coupling strategies between the Ab and drug. Efforts are continuing to develop more efficient cytotoxic payloads in third-generation ADCs so that a smaller amount of drug is needed to achieve the desired therapeutic effect and to eliminate drug resistant tumor cells. The development of PBDs, derivatives of tricyclic antibiotics, has attracted interest over other DNA alkylating agents. PBDs are potent compounds, some of which have subpicomolar IC50 and do not show cross-resistance with other chemotherapeutics, such as cisplatin. Four PBD-containing ADCs are currently in clinical trials: SC16LD6.5 is in Phase II trials for small cell lung carcinoma; SGN-CD33A is in Phase II trials for AML; SGN-CD70A is used to treat patients with CD70-positive cancer, and ADCT-301 is in Phase I trials for CD25 lymphoma (Sau S, Alsaab HO, Kashaw SK, Tatiparti K, Iyer AK. Advances in antibody-drug conjugates: a new era of targeted cancer therapy. *Drug Discov Today.* 2017 Jun 13. pii: S1359-6446(17)30078-8. doi: 10.1016/j.drudis. 2017.05.011. [Epub ahead of print]

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