«REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME OR PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS? A CHALLENGING DIFFERENTIAL DIAGNOSIS»

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Reversible cerebral vasoconstriction syndrome (RCVS) is characterised by severe recurrent thunderclap headaches, often accompanied by nausea, vomiting, photophobia, confusion, blurred vision. It is possibly caused by a transient dysregulation of cerebral vascular tone, leading to diffuse multiple segmental reversible constriction of cerebral arteries; the major complications are localized convexity nonaneursymal subarchnoid hemorrage (22%) and ischemic stroke or intracerebral hemorrhage (7%). The mean age of onset is 42 years and it affects more women than men. The syndrome is generally self-limited and has a low incidence of recurrence.

Primary central nervous system vasculitis (PCNSV) is an inflammatory disease affecting the small and medium-sized leptomeningeal and intracranial vessels. The incidence of primary CNS vasculitis in USA was estimated to be 2-4/1.000.000 person-year, it has the same frequency in men and women, median age at diagnosis is fifty. It is heterogeneous in presenting characteristics and therapeutic requirements. The size of vessels involved in inflammatory process seems to be responsible for many of these different characteristics: rapidly progressive PCNSV patients with the angiographic presence of bilateral, multiple, large vessels lesions and MRI evidence of multiple cerebral infarctions often have fatal outcomes and represent the worst end of the clinical spectrum of PCNSV, while angiography-negative patients with the involvement of small cortical and leptomeningeal vessels and MRI evidence of prominent leptomeningeal enhancement have more benign disease that responds favorably to treatment. It has been considered a life-threatening condition and most patients showed a favourable response to glucocorticoids alone or in combination with cyclophosphamide; however, there is the presence of a subgroup of patients with more serious widespread neurological lesions that are associated with poor outcome despite the treatment. Cerebrospinal fluid analysis is abnormal in 80-90% of patients: changes consist of a mildly increased leucocyte count and total protein concentration.

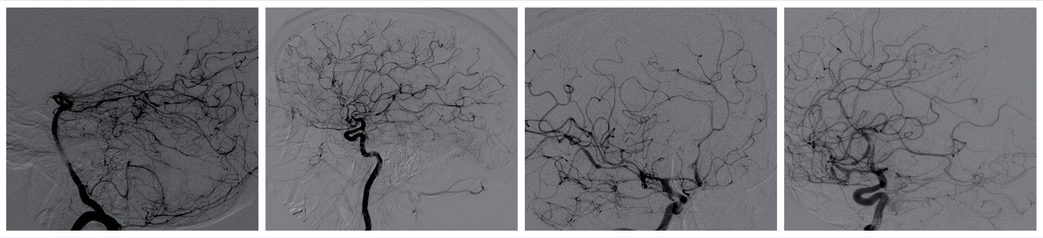
Distinction between both disorders is challenging and essential for management; cerebral and meningeal biopsy remains the gold standard for diagnosis; anyway, diagnosis is not always possible.

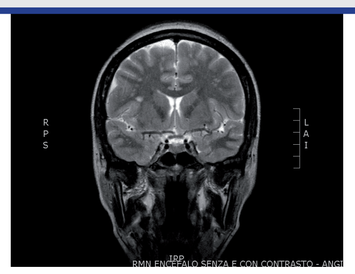
CASE REPORT

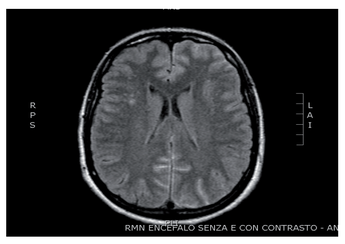
A 42 years-old Dominican woman was admitted to our department for acute onset of a rapidly progressive fronto-temporal headache, accompanied by nausea and vomiting, that was precipitated by Valsalva manoeuvre. She had no anamnestic history: no recent trauma, infections, or headache history. On admission, neurologic examination was normal, blood tests were unremarkable except for mild leukocytosis. Subarchanoid hemorrhage was ruled out by a computed tomographic scan of the brain and cerebrospinal fluid (CSF) examination. Brain MRI/MRA, performed five days after headache onset, showed bilateral frontal lobe white matter hyperintensities of presumed vascular origin along with likely right posterior communicating artery hypoplasia.

Abdominal ultrasonography, echocardiography and carotid ultrasound were normal.

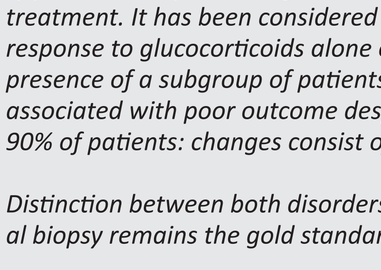
Nine days after the headache onset, the patient developed a progressive right hemiparesis and the brain CT scan showed a left fronto-parietal intracerebral hemorrhage along with cortical SAH. A new brain MRI/MRA and MR venography were normal (right PCA hypoplasia). Laboratory testing, including coagulation tests, immunological and rheumatological tests were normal. We decided to performe digital subtraction angiography (DSA) that showed arterial constriction and dilatation affecting intracranial arteries and their proximal branches (sausage on a string appearance), consistent with vasculitis. We hypothesized a PCNSV and we introduced intravenous steroid therapy (methylprednisolone 1000 mg) combined to Nimodipine. In the next days there was no clinical improvement and Cyclophosphamide was started (100 mg daily). A follow-up brain CT scan, that was performed 19 days after headache onset, showed new ischemic lesions located between the cortical territories of the anterior cerebral artery. Transcranial Doppler ultrasonography (TCD) showed diffuse increased blood flow velocities in intracranial arteries. Cerebral vasoconstriction syndrome was suspected. The patient was admitted to the intensive care unit with gradual clinical deterioration. She deceased 21 days after symptoms onset, despite two decompressive craniectomies.



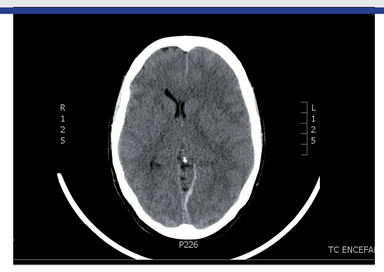


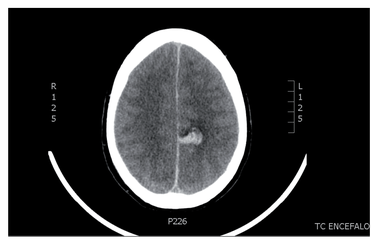


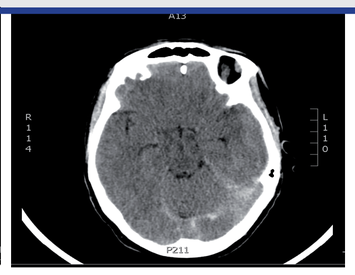
21/04/2016 *RMN ENCEFALO*
Frontal lobe white matter hyperintensities of presumed vascular origin along with likely right posterior communicating artery hypoplasia



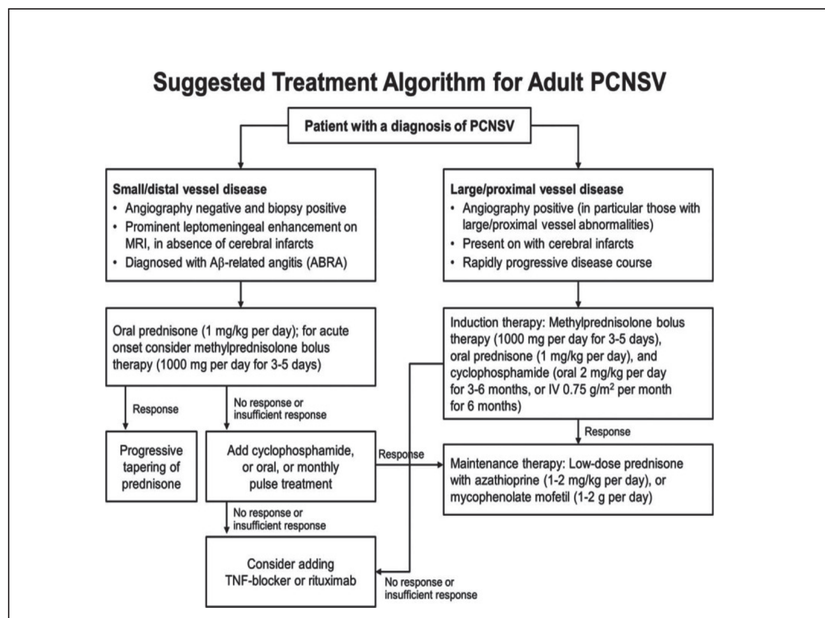
29/04/2016 *TAC ENCEFALO*



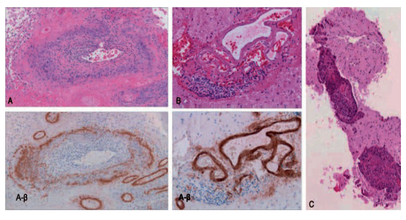




25/04/2016 *TAC ENCEFALO*
Left fronto-parietal intracerebral hemorrhage along with cortical SAH



RCVS (Reversible Cerebral Vasoconstriction Syndrome)		*PCNSV(Primary Central Nervous System Vasculitis)*	
MEAN AGE	43 yo	*MEAN AGE*	50 yo
SEX DISTRIBUTION (FEMALE/MALE)	2.4/1	*SEX DISTRIBUTION (FEMALE/MALE)*	Women are slightly more ofte affected than men (55%)
HEADACHE	Frequency: 90-100% Acute onset, often thunderclap	*HEADACHE*	Frequency: 60% Subacute and progressive (55% Cognitive dysfunction)
PRECIPITATING FACTORS	50% after exposure to vasoactive drugs or post partum	*PRECIPITATING FACTORS*	None
COURSE	Monophasic, self-limited within 1-3 months	*COURSE*	Progressive with frequent appearance of cerebral infarcts
CSF	Usually Normal (>90%)	*CSF*	Usually Abnormal (80-90%) (white cell count and total protein concentration mildly increased)
MRI	Often normal during the first week (>60%); MRA reveals diffuse segmental arterial costriction in up to 90% after 1-2 weeks	*MRI*	Abnormal in almost all patients
TYPE OF LESIONS	In the first week after onset may be complicated by SAH or ICH; in the second week ischemic lesions may occur, typically in the watershed zone (80%);	*TYPE OF LESIONS*	Small infarcts in grey and white matter in multiple vascular territories, diffuse white matter lesions, mass lesions
ANGIOGRAPHY	Always abnormal; "strings of beads" or "sausage on a string" appearance of cerebral arteries;	*ANGIOGRAPHY*	Usually abnormal (88%), Irregular and asymmetrical arterial stenoses or multiple occlusions
CNS BIOPSY	No vasculitic changes	*CNS BIOPSY*	Usually consistent of vasculitis (70%) Granulomatous Angitis (60%)
DRUG TREATMENT	Nimodipine many patients fully recover with few if any sequelae (70%)	*DRUG TREATMENT*	Prednisone with or without cytotoxic agents, response rates were 81%, relapses and recurrences 26%



Pathological findings in primary central nervous system vasculitis and cerebral amyloid angiopathy-related inflammation (CAA-RI). (A) Granulomatous pattern with amyloid angiopathy (ABRA). Transmural inflammation, often granulomatous, associated with vascular wall disruption (upper; hematoxylin and eosin [H&E] stain) and amyloid-ß deposition (lower; immunoperoxidase stain for ßA4 amyloid) is typical of ABRA. (B) CAA-RI pattern. Mild perivascular inflammation often with giant cells surrounding leptomeningeal and cortical small vessels (upper; H&E stain) with vascular amyloid deposition (lower; immunoperoxidase stain for ßA4 amyloid) is characteristic of CAA-RI. (C), Necrotizing pattern. A segment of intraparenchymal muscular artery shows extensive mural necrosis with karyorrhetic debris and acute neutrophilic inflammation (H&E).

DISCUSSION

In this case, the acute, progressive headache in a young woman along with the normal initial brain neuroimaging, intraparenchimal hemorrhage with subaracnoid hemorrhage as first cerebrovascular lesion and a normal CSF make the hypothesis of RCVS more likely; the syndrome typically follows a benign course; however, reversible cerebral vasoconstriction syndrome may result in permanent disability or death in a small minority of patients.

Glucocorticoid steroids have been administered to patients with RCVS, without improvement in either patient symptoms or sequelae of the disease.

Even if some case series have even suggested that steroid therapy may be associated with worse outcomes in RCVS, we first considered primary angiitis of the central nervous system and we promptly started steroid theraphy, because of its high rates of morbidity and mortality if left untreated.

Anyway, we think that it won't ever be possible to know what the patient have had, because she didn't undergo to cerebral and meningeal biopsy which still remains the gold standard for diagnosis.

CONCLUSION

Reversible Cerebral Vasoconstriction Syndrome (RCVS) may present as thunderclap headache (TCH), accompanied by reversible cerebral vasospasm and focal neurological deficits, often without a clear precipitant. RCVS may be mistaken for Primary Angiitis of the Central Nervous System (PACNS) due to the presence of similar angiographic features of segmental narrowing of cerebral arteries. In the high suspicious of RVCS or PACNS, biopsy should be more often taken in consideration and, if death occurs before the follow-up studies are completed, postmortem biopsy rules out such conditions as vasculitis.

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