eNeurologicalSci 6 (2017) 51–54

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: http://ees.elsevier.com/ensci/

Review article

Isolated pons involvement in Posterior Reversible Encephalopathy Syndrome: Case report and review of the literature

Ferrara Mariangela [a,*], Di Viesti Pietro [a], Inchingolo Vincenzo [a], Latino Raffaela Rita [a], Popolizio Teresa [b], De Cosmo Salvatore Angelo [c], Pugliese Flavia [c], Leone Maurizio Angelo [a]

[a] Neurology Unit, Department of Medicine, Research Center "Casa Sollievo della Sofferenza", San Giovanni Rotondo, FG, Italy
[b] Radiodiagnostics Department, Research Center "Casa Sollievo della Sofferenza", San Giovanni Rotondo, FG, Italy
[c] Endocrinology Unit, Department of Medicine, Research Center "Casa Sollievo della Sofferenza", San Giovanni Rotondo, FG, Italy

ARTICLE INFO

Article history:
Received 31 July 2016
Received in revised form 18 November 2016
Accepted 21 November 2016
Available online 28 November 2016

Keywords:
A typical Posterior Reversible Encephalopathy Syndrome
Infratentorial vasogenic oedema
Pontine oedema
Clinico-radiological dissociation

ABSTRACT

Background: Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical-radiological syndrome, usually reversible and with a favorable prognosis, which recognizes a variety of etiologies and clinical patterns and is likely due to an impairment in cerebral blood flow autoregulation. It is typically characterized by subcortical, predominantly parieto-occipital, vasogenic brain oedema in patients with acute-subacute neurological symptoms. Infratentorial oedema on neuroimaging has been mostly described in association with the typical supratentorial pattern and seldom as isolated.
Case report: We report a case of PRES with isolated pons involvement on MRI. A woman affected by Turner syndrome, epilepsy, slight mental deficiency, obesity and hypothyroidism, experienced a progressive gait and standing impairment, worsening in the last 2 weeks. At admission blood pressure was 220/110 mmHg. Brain MRI showed a wide FLAIR signal hyperintensity on T2-weighted sequences affecting the entire pons, without contrast enhancement. Clonidine, doxazosine, furosemide and telmisartan were effective in restoring normal blood pressure. Pons hyperintensity completely resolved on MRI 3 weeks later, together with return to normal neurological examination.
Conclusions: Though isolated infratentorial involvement in PRES recognizes several causes, hypertension, which is a common feature in Turner syndrome, would have played a key role in our case with solely pons MRI T2-hyperintensity.

Contents

1. Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical condition likely sustained by an impaired neurovascular unit autoregulation of the cerebral blood flow which, in turn, leads to endothelial dysfunction and vasogenic brain oedema. It recognizes different etiologies. Clinical presentation varies widely for both features and severity across reported case series and, at times, does not match either with the pattern or the amount of brain oedema on MRI [1]. Bartynski WS et al. [2] reported three major patterns consistent for typical PRES imaging: holohemispheric watershed (linear vasogenic oedema at anastomotic border zone spanning the frontal, parietal and occipital lobes with lesser temporal lobes involvement), superior frontal sulcal (involvement of the frontal lobe along the mid to posterior aspect of the

* Corresponding author at: Neurology Unit, Department of Medicine, Research Center "Casa Sollievo della Sofferenza", viale Cappuccini, 1, 71012 San Giovanni Rotondo, FG, Italy
E-mail address: mariangela.ferrara@operapadrepio.it (M. Ferrara).

http://dx.doi.org/10.1016/j.ensci.2016.11.008

superior frontal sulcus with no frontal pole extension) and dominant parietal-occipital (vasogenic oedema of the parietal and occipital cortex and white matter, variably extended to the temporal lobes). Partial or asymmetric expressions of the primary patterns (with, respectively, bilateral or unilateral absence of signal hyperintensity in either the parietal or occipital lobes) are possible. Brainstem involvement is infrequent and usually associated with the typical subcortical parietal-occipital bilateral sites of T2 hyperintensity [3].

2. Case description

A 28 years-old woman, affected by Turner syndrome, epilepsy treated with oxcarbazepine 600 mg/day, slight mental deficiency, obesity and hypothyroidism in therapy with levothyroxine 125 μgr/day, was admitted with a progressive gait and standing impairment, worsening in the last 2 weeks. She had experienced episodes of tachycardia and acute hypertensive crisis in the past years, although blood pressure monitoring and 24-hour electrocardiogram were normal at that time. She was in ovarian hormone replacement treatment (gestodene 0.075 mg + ethinyl estradiol 0.03 mg/day). At admission blood pressure was 220/110 mmHg with heart rate of 120 bpm. Neurological examination showed inability at standing and walking, paraparesis, brisk reflexes at four limbs, and bilateral Babinski sign. Sensitivities were intact. The patient was confused but alert. Furosemide 25 mg was rapidly administered by infusion and transdermal patch clonidine 2.5 mg/week was prescribed. She underwent full blood examination (complete blood count, electrolytes, liver and kidney function, homocisteine, folate, B12 vitamin, vanilmandelic acid and chromogranine A levels, serum and urinary catecholamines and metanephrines, antiviral, bacterial, thrombophilic and autoimmune screenings), CSF examination, abdominal, renal arteries and cardiac ultrasound examinations (searching for causes of secondary arterial hypertension), thoracic aorta MRI (searching for aortic bicuspid valve or aortic arch abnormalities, typical in Turner syndrome, or possible dissecation). All these examinations were normal. Oxcarbazepine dosage and thyroid hormones were in range. 24-hour electrocardiogram showed sinusal tachycardia. A brain MRI at admission showed a wide FLAIR hyperintensity on T2-weighted sequences affecting the entire pons, without contrast enhancement (Fig. 1).

Ovarian hormone replacement treatment was suspended. Clonidine transdermic patch 2.5 mg/week, doxazosine (tapering slowly up to 6 mg/day), furosemide (up to 50 mg/day) and telmisartan (80 mg/day) were effective in restoring normal blood pressure within 10 days together with concomitant return to normal neurological examination. Notably, at present, neither specific antihypertensive drug has been formally studied for the treatment nor randomized clinical trials assessing therapeutic interventions in PRES have been undertaken [1]. The selection of drugs is left to the discretion of the physician and our initial therapeutic goal was to reduce blood pressure by 25% within the first few hours, as recommended [4]. Beta-blockers for sinus tachycardia were initially delayed whereas possible neoplasm of chromaffin tissue was investigated. Repeated serum and urinary dosages of catecholamines, metanephrines, and vanilmandelic acid were normal 2 weeks after admission. A metaiodobenzylguanidine scintigraphy was performed to exclude a paraganglioma-pheochromocytoma and resulted normal. Then atenolol 50 mg/day was introduced successfully.

Pons hyperintensity was completely resolved on MRI performed 3 weeks after admission (Fig. 2).

3. Discussion

PRES with isolated pons involvement has been rarely described [5–10] and only small series in the form of isolated pontine T2 hyperintensity on MRI have been reported [7]. Severe arterial hypertension alone [5] or in association with acute renal failure [7], highly active antiretroviral therapy [6,10] and oxaliplatinum chemotherapy [9] have been described as precipitating factors in clinical settings of chronic renal failure [7,8], arterial hypertension [5], AIDS [6,10] and cancer [9]. To date, a review of seven brainstem PRES by Gao et al. [7] listed only one case with isolated pons lesion and spared supratentorial involvement. In this case dizziness and weakness were reported as clinical features in the context of arterial hypertension and chronic renal failure. The remaining six brainstem PRES cases in Gao and coll. showed a relatively mild clinical presentation wherein, apart from a case with coma, dizziness and instability were most commonly described. To our knowledge, only seven cases of pontine PRES has been published so far, as reported in Table 1.

Overall, they show a dissociation between the mild clinical features, mostly not referable to the brainstem, and the severity of the MRI images [11–14]. This pattern of *clinico-radiological dissociation* may be considered a key feature of brainstem PRES, and represents a clue for

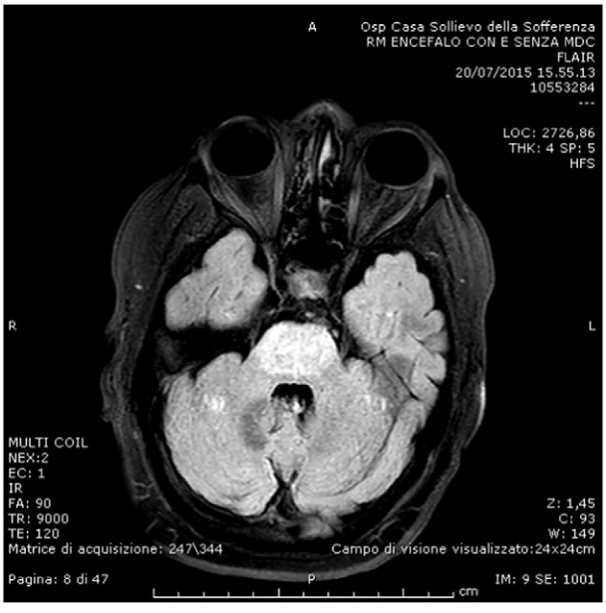

Fig. 1. Isolated involvement of the entire pons in FLAIR sequences at entry MRI.

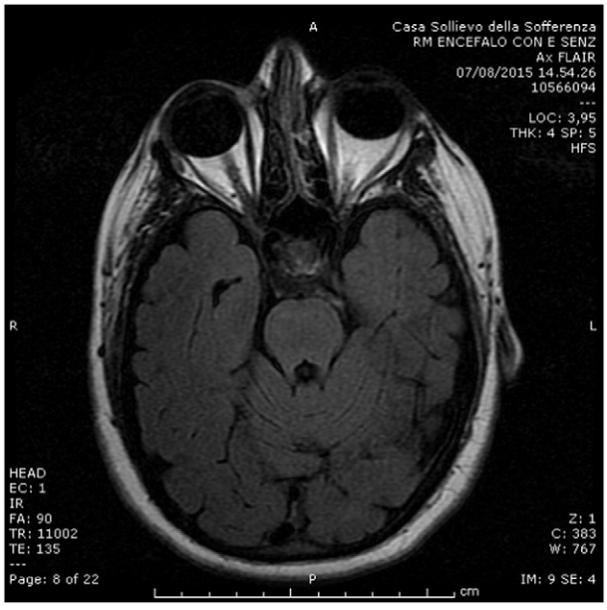

Fig. 2. Complete resolution of pontineT2-hyperintensity at control MRI, after antihypertensive treatment and neurological recovery.

Table 1
Clinical features of 7 cases with isolated pons involvement in PRES reported in literature.

Case no.	Author (year)	Age (years)	sex	BP (mmHg)	Precipitating cause	Clinical setting	Symptoms/signs	Outcome
1	Gamanagatti S et al. (2006)	60	M	220/150	SHT	None	Unconscious state, bilateral papilloedema	R
2	Tanioka R et al. (2007)	44	M	ranging from 130/75 to 96/50	HAART + helminth infection treated with metronidazol	AIDS	Mild psychiatric symptoms	R
3	Gao B et al. (2012), case no 7	30	M	190/100	SHT, ARF	CRF	Dizziness, weakness of right limbs	R
4	Liang H et al. (2013)	36	F	260/140	SHT, IS	Newly diagnosed PSG with IgA nephropathy	Nausea, vomiting, right-sided weakness, right hemiparesis, Babinski sign	R
5	Tang KH (2015)	81	M	140/85	Oxaliplatin therapy	MCC	Altered mental status, drowsiness	R
6	Cartier L et al. (2016)	25	M	described as normal	HAART	AIDS	Dizziness, postural instability, nistagmus	R
7	Present case	28	F	220/110	SHT, OHRT	TS	Gait and standing impairment, paraparesis, brisk reflexes at four limbs, bilateral Babinski sign	R

PRES Posterior Reversible Encephalopathy Syndrome, *M* male, *SHT* severe hypertension, *R* resolution, *HAART* highly active antiretroviral therapy, *AIDS* acquired immune deficiency syndrome, *ARF* acute renal failure, *CRF* chronic renal failure, *F* female, *IS* ischemic stroke, *PSG* proliferative sclerosing glomerulonephritis, *MCC* metastatic colorectal carcinoma, *OHRT* ovarian hormone replacement treatment, *TS* Turner syndrome.

diagnosis and differentiation from typical PRES, the latter being associated to encephalopathy, seizures, status epilepticus, headache, visual disturbances and focal findings [1], usually with typical MRI imaging pattern [2].

Four out of 7 pontine PRES reported in Table 1 showed severe hypertension as precipitating factor [5,7,8] in the clinical context of renal diseases in 2 cases [7,8] and apparently isolated in 1 case [5]. Renal failure is a classic disorder associated with PRES but whether it is an independent or a concurrent risk factor along with hypertension or autoimmune disorders is still unknown [1]. On the other hand, Liang et al. postulates that chronic renal failure, a well known risk factor for atherosclerotic disease, could determine PRES by participating to endothelial dysfunction in cerebral small vessels together with the acute increasing of vasoreactivity, hypertension-mediated [8]. Notably, patients with chronic kidney disease might also develop PRES with only a mild elevation of blood pressure because of electrolyte imbalance and protein urinary loss [15].

Our patient showed severe hypertension at admission likely linked to her Turner syndrome, and possibly precipited by the ovarian hormone replacement treatment. High blood pressure is actually reported in 13–58% of adults with Turner syndrome [16] and is presumably multifactorial. Interestingly, Turner syndrome is characterized by functional dysregulation of sympathetic nervous system and oxidative stress, both bringing to endothelial dysfunction and reduced vessel distensibility [16], which would be relevant in determining PRES.

Two cases in Table 1 are associated to acquired immune-deficiency syndrome. It is well known that HIV-1 infection can lead to vascular diseases by three pathogenetic mechanisms: direct HIV-1 mediated damage of vascular endothelium and associated chronic inflammation due to HIV-1 replication, side effects/off target effects from antiretroviral pharmacotherapy, changes in traditional risk factors such as tobacco abuse and dyslipidemia [17]. HIV-1 has long been known to directly injure the vascular endothelium inducing high secretion of some cytokines and growth factors by monocytes, macrophages and lymphocytes. These growth factors and cytokines can lead to dysregulation of endothelial and vascular smooth muscle cell growth and imbalance of endogenous vasodilators and constrictors (in favor of constrictors) [18]. Moreover, highly active antiretroviral therapy (HAART) can increase endothelial oxidative stress through escalated generation of reactive oxygen/nitrogen species (ROS/RNS) and impact the functional integrity of blood-brain barrier microvascular endothelium [19]. In these 2 cases reported in Table 1 both direct pathogenetic mechanisms of HIV-1 and side effects of antiretroviral therapy could have determined PRES, increasing cerebrovascular permeability and causing vasogenic oedema. Furthermore, the concomitant helminth infection in Case no 2 might have favored the release of additional mediators with increase of vascular permeability.

In the case reported by Tang [9], PRES could be presumably due to the oxaliplatin upregulation of vascular endothelial growth factor (VEGF) mRNA expression and VEGF receptors in human colorectal cancer cells [20]. In fact, circulating VEGF can promote vascular permeability and the development of interstitial oedema in PRES [1]. Expression of VEGF is regulated by several mediators and environmental conditions, one of the most potent being hypoxia which, actually, promotes signalling cascades to upregulate VEGF-A expression with final vasodilation and angiogenesis [20]. Interestingly, increased concentrations of VEGF-A have been observed in pre-eclampsia and eclampsia, both associated with PRES [1]. Furthermore, excessive circulating cytokines, a condition that typically accounts for endothelial dysfunction in autoimmune disorders and sepsis, can induce VEGF. These latter have been both reported as clinical conditions in PRES [1].

The underlying mechanism of a selective pontine involvement with sparing supratentorial lesions in PRES is not fully understood. In some susceptible patients acute hypertension, or pronounced fluctuations of blood pressure (like in hypotension and sepsis), could influence a breakdown in the blood-brain barrier with subsequent vasogenic oedema. The vertebro-basilar system is considered more vulnerable to imbalanced perfusion pressure because of its defective sympathetic-mediated vasocostriction which may have a protective role [1]. In a retrospective observational study aimed to correlate MRI patterns to clinical manifestations in PRES [21], the term *central-variant PRES* was introduced for a pattern, typically associated with severe hypertension, of selective vasogenic brainstem and basal ganglia oedema with sparing subcortical parietal-occipital white matter. According to authors, brain oedema prevalent in the supratentorial white matter correlates to moderate hypertension values, whilst an infratentorial involvement would account for cases with a prolonged history of persistent severe hypertension [21]. In a more recent retrospective observational study [22], the same authors tried to determine which structures are involved in the central variant of PRES and to describe the causes associated with this imaging pattern. Out of 124 PRES cases only 5 central-variant were sought, brainstem being involved in all of them. The causes of PRES in these five patients were hypertension (N = 2), immunosuppressive medication (both cyclosporine, N = 2), and eclampsia (N = 1). The authors ended up hypothising that a possible underlying mechanism for *central variant PRES* could be an increased sensitivity to endothelial cell dysfunction within smaller, perforating vessel supplying the brainstem from a cause not yet known. From this perspective, since the selective pattern of pontine involvement on MRI for central-variant PRES is quite uncommon and possible causes are many, a careful

differential diagnosis is required. Our patient, in particular, showed a relatively mild clinical presentation without major brainstem signs despite the extensive radiological pattern of lesion. Symptoms didn't show a sudden onset but had been progressing over two weeks and features of vasogenic oedema on neuroimaging at entry with a complete resolution with no lesion in DWI and no restricted diffusion in the ADC map at control excluded pontine ischemia. Regression of signal hyperintensity in T2-weighted sequences at control MRI ruled out possible space-occupying mass, such as glioma, as well. Lacking fever both on the days before and at the time of symptoms onset, no contrast enhancement on MRI and the absence of CSF and blood chemistry abnormalities allowed to reject the hypothesis of possible acute demyelinating encephalomyelitis. Medical history and laboratory data have also disproved the hypothesis of an infectious episode of the brainstem. Finally, the isolated pontine lesion on MRI could lead to the suspicion of central pontine myelinolysis, but, the absence of hyponatremia at entry (hypothetically facilitated by oxcarbazepine intake) and at follow-up and a more extensive radiological pattern of pons involvement rather than a central selective one, ruled out that assumption.

4. Conclusions

Central-variant should be considered an atypical pattern of PRES presentation with clinical-radiological dissociation possibly being the clue feature. All the seven pontine PRES cases reviewed here showed this fashion and severe hypertension acts as the more frequent precipitating factor. Isolated pontine involvement in neuroimaging is rare and, provided a correct identification of the precipitating causes, a complete clinical and radiological recovery was observed in all cases. Pontine localization can be very tricky and an accurate differential diagnosis must be sort out amongst a heterogeneous list of possible causes: to this regard ADC map and DWI sequences of MRI scans at onset and after recovery play an important role in distinguishing the vasogenic oedema from other possible entities. Physiopathogenetic mechanisms underlying PRES are not completely understood as the disease is described in a wide number of clinical contexts: nevertheless a possible peculiar poor pattern of vertebro-basilar sympathetic innervation of the brainstem along with an impaired neurovascular unit mechanism of cerebral blood flow autoregulation at different etiologies could be hypothised.

Conflict of interest

The authors declare that there are no conflicts of interest.

References

[1] J.E. Fugate, A.A. Rabinstein, Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions, Lancet Neurol. 14 (2015) 914–925.
[2] W.S. Bartynski, J.F. Boardman, Distinct imaging patterns and lesion distribution in posterior reversibile encephalopathy syndrome, Am. J. Neuroradiol. 28 (2007) 1320–1327.
[3] H. Kitaguchi, H. Tomimoto, Y. Miki, et al., A brainstem variant of reversibile posterior leukoencephalopathy syndrome, Neuroradiology 47 (2005) 652–656.
[4] G. Mancia, R. Fagard, K. Narkiewicz, et al., 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), Eur. Heart J. 34 (2013) 2159–2219.
[5] S. Gamanagatti, S. Subramanian, Hypertensive encephalopathy: isolated pons involvement mimicking central pontinemyelinolysis, Korean J. Radiol. 7 (2006) 3.
[6] R. Tanioka, et al., Convalescence of atypical reversible posterior leukoencephalopathy syndrome in human immunodeficiency virus infection, J. Med. Investig. 54 (2007) 191–194.
[7] B. Gao, H. Liang, F. Liu, et al., Isolated pons involvement in posterior reversibile encephalopathysyndrome in patient with chronic renal insufficiency: case report and literature review, Clin. Neuroradiol. 22 (2012) 341–344.
[8] H. Liang, D. Li, Z. Xu, et al., Isolated pons variant of posterior reversible encephalopathy syndrome complicated with ischemic stroke in a yuong patient, Neurol. Sci. 34 (2012) 1082.
[9] K.H. Tang, Oxaliplatin-induced posterior reversible encephalopathy syndrome with isoltaed involvement of pons, J. Cancer Res. Ther. 11 (2015) 1022.
[10] L. Cartier, J.M. Matamala, A. Yanez, et al., Rev. Med. Chil. 144 (2016) 675–679.
[11] R.T. Fitzgerald, R.S. Samant, M. Kumar, et al., Features of infratentorial-predominant posterior reversible encephalopathy syndrome, Acta Neurol. Belg. 115 (2015) 629–634.
[12] S. Shintani, T. Hino, S. Ishihara, et al., Reversible brainstem hypertensive encephalopathy (RBHE) clinicoradiologic dissociation, Clin. Neurol. Neurosurg. 110 (2008) 1047–1053.
[13] M. Thambisetty, V. Biousse, N.J. Newman, Hypertensive brainstem encephalopathy: clinical and radiographic features, J. Neurol. Sci. 208 (2003) 93–99.
[14] F. Morello, A. Marino, M. Cigolini, et al., Hypertensive brain stem encephalopathy: clinically silent massive edema of the pons, Neurol. Sci. 22 (2001) 317–320.
[15] B. Gao, L. Cv, Central-variant posterior reversible encephalopathy syndrome: more than meets the eye, AJR 203 (2014) (p. W454 0361–803X/14/2034–W454).
[16] K. De Groote, L. Demulier, J. De Backer, et al., Arterial hypertension in Turner syndrome: review of the literature and a practical approach for diagnosis and treatment, J. Hypertens. 33 (2015) 1342–1351.
[17] C.T. Lambert, et al., HIV, highly active antiretroviral therapy and heart: a cellular to epidemiological review, HIV Med. 17 (2016) 411–424.
[18] J.J.R. Bigna, et al., HIV related pulmonary arterial hypertension: epidemiology in Africa, physiopathology, and role of antiretroviral treatment, AIDS Res. Ther. 12 (2015) 36.
[19] S. Prasad, et al., Hyperglycemia exacerbates antiretroviral drug combination induced blood-brain barrier endothelial toxicity, Neurotoxicology 56 (2016) 1–6.
[20] F. Fan, et al., Effect of chemotherapeutic stress on induction of vascular endothelial growth factor family members and receptors in human colorectal cancer cells, Mol. Cancer Ther. 7 (2008) 9.
[21] A.M. McKinney, J. Short, C.L. Truwit, Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings, AJR Am. J. Roentgenol. 189 (2007) (p. 904–903).
[22] A.M. McKinney, B.D. Jagadeesan, C.L. Truwit, Central-variant posterior reversible encephalopathy syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical cerebral edema, AJR 201 (2013) 631–638.