J Neurol (2011) 258:1176–1179
DOI 10.1007/s00415-011-5903-6

LETTER TO THE EDITORS

Acute pulmonary edema caused by a multiple sclerosis relapse

P. Wipfler · G. Pilz · E. Broussalis · S. M. Golaszewski · A. Kunz · E. Trinka · J. Kraus

Received: 9 November 2010 / Revised: 30 December 2010 / Accepted: 3 January 2011 / Published online: 1 February 2011

Dear Sirs,

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) [1]. In the majority of patients, MS begins with a relapsing–remitting course. It is characterized by unpredictable relapses followed by periods of months to years of clinical remission. MS relapses entail various clinical symptoms depending on the location of the inflammatory lesion within the CNS. Besides the common symptoms of optic neuritis, paresis, paraesthesia, and ataxic gait disorders, in some rare cases a relapse may alter cardiovascular and autonomic function [1]. Clinical studies have shown that acute cerebral lesions (e.g., stroke, hemorrhage) may induce changes in cardiac and respiratory function including hypertension, arrhythmias, myocardial necrosis, and sudden death [2, 3]. Moreover, experimental and clinical studies indicate that damage of the brainstem is likely to cause disturbances in either sympathetic or parasympathetic autonomic function with subsequent cardiac and respiratory dysfunction [4–6]. Neurogenic pulmonary edema (NPE) is usually defined as an acute pulmonary edema occurring shortly after various injuries of the central nervous system [7]. The most important vasomotor centers for NPE development are nuclei of the solitary tract, the dorsal motor vagus nucleus in the medulla oblongata and the medial reticulated nucleus. On the other hand, brainstem damage in the region of the solitary tract nuclei may result in a transient cardiomyopathy [8]. The exact mechanisms remain poorly understood because of the complexity of its pathophysiologic mechanisms, involving both hemodynamic and inflammatory aspects. There are two possible explanations: one presumes that neurological damage directly involves the pulmonary and cardiac vascular bed with disconnection of the central nervous system vasomotor centers. However, there are also data that brainstem dysfunction can cause changes of sympathetic vasomotor tone [7]. This case study describes a rare initial presentation of a MS relapse with pulmonary edema caused by left ventricular failure.

A 48-year-old woman, diagnosed with clinically definite relapsing–remitting MS 3 years previously with a preexisting expanded disability status scale (EDSS) of 3.5, presented with increasing dyspnea and cough without chest pain to a department of internal medicine. She was on immunomodulatory treatment with glatiramer acetate. No clinically apparent atherosclerotic disease was known. On admission, laboratory testing showed that high-sensitivity troponin T was slightly elevated. An electrocardiogram showed no signs of myocardial infarction. In a coronary computed tomography angiogram, no significant changes in the coronary arteries were found. The next day, increases in high-sensitivity troponin T, C-reactive protein (CRP), and a massive increase of B-type natriuretic peptide (proBNP) were observed (Table 1). Pulmonary edema was initially not diagnosed (Fig. 1a) and according to the assumption of pneumonia the patient was treated with antibiotic therapy (amoxicillin) and furosemide. Due to the further worsening of respiratory conditions, intubation and mechanical respirator treatment became necessary. An echocardiogram showed acute left ventricular failure with apical wall motion abnormalities and a left ventricular ejection fraction of 35% in this patient without a history of cardiac disease. No abnormalities concerning the right ventricle and the atria were seen. With regard to her

P. Wipfler (✉) · G. Pilz · E. Broussalis · S. M. Golaszewski · A. Kunz · E. Trinka · J. Kraus
Christian-Doppler-Klinik, University Hospital of Neurology, Paracelsus Medical University and Salzburger Landesklinken, Ignaz Harrerstrasse 79, 5020 Salzburg, Austria
e-mail: p.wipfler@salk.at

underlying disease and to the significant deterioration of her condition despite antibiotic therapy, a neurologist was consulted. Neurological examination showed left-sided hemiparesis and a facial nerve paresis on the right side. Brain MRI demonstrated a hyperintense lesion in T2-weighted images with surrounding parasagittal, right-sided edema within the right upper medulla oblongata indicating an acute demyelinating lesion with slight contrast enhancement in T1-weighted images (Fig. 1b, c). The axial T2-weighted image showed the anatomical location of the lesion in relation to nuclei of known importance for the development of NPE (nucleus of the solitary tract, reticular formation, and dorsal motor nucleus of the vagus nerve) (Fig. 1d).

Assuming that the pulmonary edema was caused by an acute left ventricular failure based upon the active inflammatory MS lesion of the brainstem, the patient was treated with high-dose methylprednisolone (1 g i.v. over 5 days). Within 2 days a significant improvement in ejection fraction (50%) of the heart and a restitution of pulmonary edema were observed. After a further 2 days, extubation was possible and only a central vertigo and a slight left-sided hemiparesis persisted. The patient's condition had improved with the cardiac enzyme levels having declined to within the nearly normal range within 5 days after the initial event. A follow-up echocardiography performed 14 days after the attack demonstrated normal wall motion of the left ventricle. The episode-related symptoms (vertigo and left-sided hemiparesis) remitted over the subsequent weeks (finally EDDS 3.5 again).

We present unusual clinical symptoms of a MS relapse with pulmonary edema due to acute left ventricular failure. The rapid improvement in ejection fraction after high-dose cortisone therapy confirms our theory that the acute left ventricular failure was caused by the active brainstem lesion.

Apical ballooning syndrome (takotsubo cardiomyopathy) is the most probable explanation for transient cardiomyopathy [9]. It was named 'takotsubo' due to the morphology of the apical ballooning of the heart that is similar in shape to a 'takotsubo', which is a pot with a round bottom and narrow neck used for trapping octopuses in Japan. This syndrome is precipitated by emotional or physical stress and is often clinically manifested as pulmonary edema. One the one hand, MS relapses are often associated with emotional or physical distress. However, persistence of cardiac failure after intubation and high-dose sedoanalgetic treatment is not consistent with the theory of cardiac failure being caused by emotional distress in our patient. One the other hand, experimental studies showed that the control of heart contractibility is located within the brainstem [10]. A recent case report about an acute disseminated encephalomyelitis associated with *Mycoplasma pneumoniae* infection shows bilateral inflammatory lesion in the dorsal medulla oblongata that preceded takotsubo cardiomyopathy, affecting both solitary tract nuclei [8]. We suggest that the transient cardiomyopathy was caused directly by the active MS lesion. The initial markedly elevated troponins and ejection fraction of 35% with improvement of cardiac enzyme levels and wall motion just a few days after the initial event support the theory of takotsubo cardiomyopathy. This syndrome mimics acute myocardial infarction with dyspnea, sometimes electrocardiographic ST segment changes, elevated troponin, and left ventricular dysfunction [9]. A further confirmation for our hypotheses of direct association with the active MS lesion in the dorsal medulla oblongata is the complete recovery of left ventricular systolic function after high-dose corticosteroid therapy.

In a previous case report of idiopathic cardiomyopathy in a patient with MS, the authors hypothesized an autoimmune origin of cardiomyopathy [11]. A statistically significant subclinical decrease of the left ventricular

Table 1 Laboratory testing (n.d. not done)

	On admission	Day 1	Day 3	Day 5	Reference values
Sodium (mmol/l)	**133**	140	140	138	135–145
Potassium (mmol/l)	**3.00**	3.7	3.9	3.8	3.50–5.10
Leukocytes (G/l)	**13.56**	**10.92**	7.49	5.62	4.30–10.00
C-reactive protein (mg/dl)	0.05	**6.0**	3.7	0.58	0.00–0.50
Creatine kinase (U/l)	54	116	45	30	26–140
High-sensitivity troponin T (ng/l)	**20**	**1053**	**655**	**91**	<14
Troponin I (μ/l)	n.d.	**3224**	n.d.	n.d.	<0.032
proBNP (pg/ml)	n.d.	**1277**	**3136**	**237**	<150
GOT (U/l)	**54**	n.d.	n.d.	n.d.	10–35
GPT (U/l)	**51**	n.d.	n.d.	n.d.	10–35
GGT (U/l)	18	n.d.	n.d.	n.d.	6–42
Creatine (mg/dl)	0.64	0.8	0.7	0.7	0.51–0.96

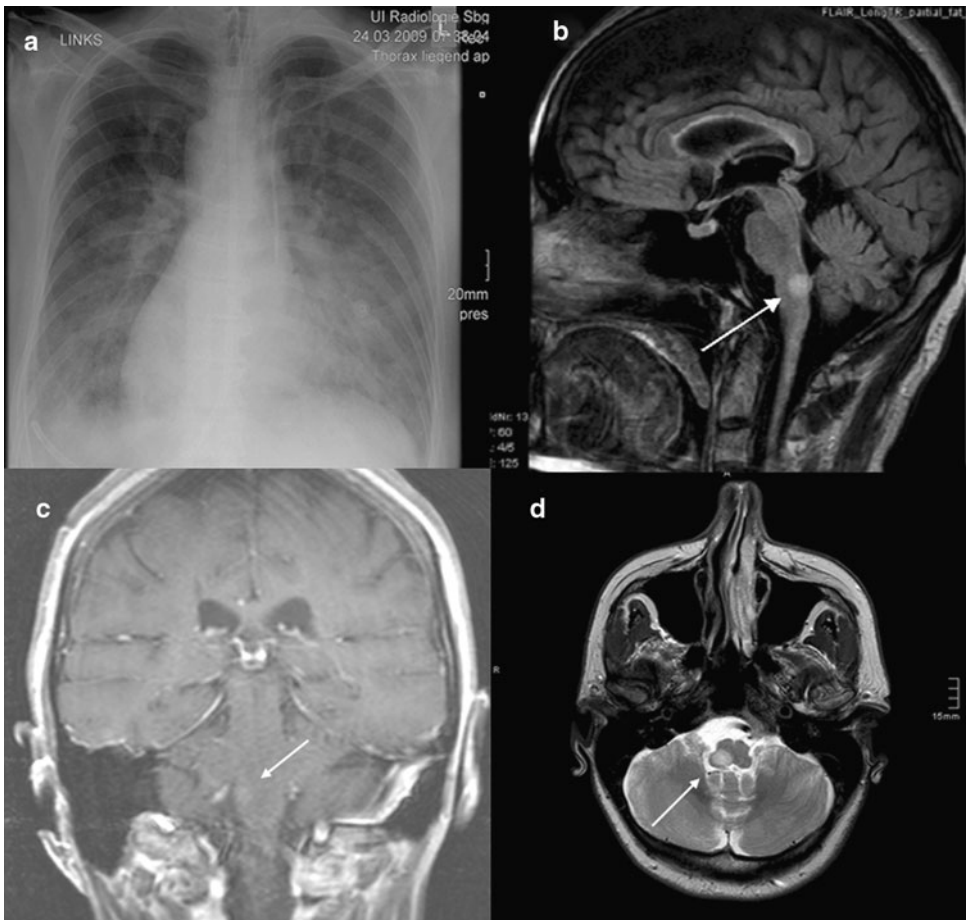

Fig. 1 **a** Extensive alveolar infiltration of both lungs with symmetrical arrangement—diagnosed as a pulmonary edema. **b** Coronal TSE T2-weighted image (TR/TE 2900/102 ms; echo train length 7; number of acquisitions 4; matrix 192 × 256; FOV 220 mm; slice thickness 5 mm; gap 0.25) showing a hyperintense round lesion with surrounding edema parasagittal right sided within the upper medulla oblongata indicating an acute demyelinating lesion (*white arrow*); **c** after the iv administration of 0.1 mmol gadopentetate dimeglumine per kg body weight, slight enhancement in the SE T1-weighted images (TR/TE 570/15 ms; number of acquisitions 5; matrix 192 × 256; FOV 220 mm, slice thickness 5 mm; gap 0.25) confirmed the assumption of acute demyelination (*white arrow*); **d** axial TSE T2-weighted image (for parameters see coronal TSE T2-weighted image) depicting the anatomical location of the lesion in relation to nuclei of known importance for the development of neurogenic pulmonary edema (nucleus of the solitary tract, reticular formation, and the dorsal motor nucleus of the vagus nerve) (*white arrow*)

ejection fraction in patients with multiple sclerosis was reported [11].

Another theory is the occurrence of neurogenic stunned myocardium. Neurogenic stunned myocardium is defined as myocardial dysfunction occurring after diverse types of acute brain injury as a result of imbalance of the autonomic nervous system [12]. Cardiac abnormalities include reversible changes both in systolic and diastolic dysfunction of the left ventricle. It remains poorly understood because of the complexity of its pathophysiologic mechanisms, involving both hemodynamic and inflammatory aspects. It should be mentioned that takotsubo cardiomyopathy and neurogenic cardiac stunning are both neurally mediated processes that share an overlapping phenotype.

Another theory is the primary NPE with secondary cardiomyopathy. The most important vasomotor centers for NPE development are the nuclei of the solitary tract, the dorsal motor vagus nucleus in the medulla oblongata, and the medial reticulated nucleus. In our case, the lesion in the nucleus of the solitary tract is possibly the cause for the NPE. It develops on the basis of a previous massive blood pressure elevation accompanied by baroreflex-induced bradycardia. The development of NPE has been shown to be preventable by prior ganglionic blockade by pentolinium, which indicates the crucial role of sympathetic hyperactivation or by the previous administration of atropine, which abolishes the baroreflex-induced bradycardia. However, the transient cardiomyopathy and initial markedly elevated troponins favor a primary cardiac genesis.

We present a case of acute left ventricular failure caused by an acute inflammatory MS lesion of the brainstem. The significant improvement in ejection fraction after high-dose

corticosteroid therapy confirms this theory. In our case, we could demonstrate the wide range of MS relapse symptoms. Clinicians should be aware of this constellation if a MS patient presents with dyspnea. The treatments should generally focus in these cases on the underlying neurologic process (MS relapse) to maximize both neurological and also cardiological recovery in such a life-threatening condition.

Conflict of interest None.

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG (2000) Multiple sclerosis. N Engl J Med 343:938–952
2. Tokgozoglu SL, Batur MK, Topcuoglu MA, Saribas O, Kes S, Oto A (1999) Effects of stroke localization on cardiac autonomic balance and sudden death. Stroke 30:1307–1311
3. Wang TD, Wu CC, Lee YT (1997) Myocardial stunning after cerebral infarction. Int J Cardiol 58:308–311
4. Oppenheimer S, Norris JW (1995) Cardiac manifestations of acute neurological lesions. In: Aminoff MJ (ed) Neurology and general medicine: the neurological aspects of medical disorder, 2nd edn. Churchill Livingstone, New York, pp 183–200
5. Meyer S, Strittmatter M, Fischer C, Georg T, Schmitz B (2004) Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. Neuroreport 15:357–361
6. Kraus J, Heckmann JG, Druschky A, Erbguth F, Neundorfer B (1999) Ondine's curse in association with diabetes insipidus following transient vertebrobasilar ischemia. Clin Neurol Neurosurg 101:196–198
7. Baumann A, Audibert G, McDonnell J (2007) Neurogenic pulmonary edema. Acta Anaest Scand 51:447–455
8. Berganzo K, Ciordia R, Go′mez-Esteban JC, Tijero B, Agundez M, Velasco F, Valle MA, Zarranz JJ (2010) Tako-tsubo cardiomyopathy in a patient with bilateral lesions in the dorsal medulla. Clin Auton Res [Epub med]
9. Chahal GS, Polena S, Fard BS, Natesan S, Sharma S, Gintautas J (2008) Takotsubo cardiomyopathy: case report and review of the literature. Proc West Pharmacol Soc 51:48–51
10. Nalivaiko E, Antunes V, Paton J (2009) Control of cardiac contractility in the rat working heart—brainstem preparation. Exp Physiol 95:107–119
11. Sellbach AN, Pender MP (2005) Multiple sclerosis with idiopathic dilated cardiomyopathy: a case report. Eur Neurol 53:214–215
12. Nguyen H, Zaroff JG (2009) Neurogenic stunned myocardium. Curr Neurol Neurosci Rep 9:486–491