

Case report

## Increased cytokine levels in a cerebral mycotic aneurysm in a child with Down's syndrome

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### Abstract

Cerebral mycotic aneurysms are one of the most serious complications of bacterial endocarditis but the mechanism underlying cerebral aneurysms is unclear. We reported the cytokine levels in a cerebral mycotic aneurysm in a child with Down's syndrome. The patient was a 12-year-old female. She was diagnosed as having Down's syndrome and congenital heart disease consisting of an endocardial cushion defect at birth. She underwent a radical operation at 9 years but mitral valve regurgitation remained. She was hospitalized with high fever, vomiting, loss of activity and gait disturbance. Neurological examination revealed facial palsy and hemiparesis on the left side. Cytokines such as IL-6, TNF- $\alpha$ , sTNFR1 and sE-selectin were elevated in blood, and IL-6, TNF- $\alpha$  and sTNFR1 in cerebrospinal fluid. T2-weighted MRI disclosed a low intensity area in the right Sylvian sulcus. MR angiography showed an aneurysm of the right middle cerebral artery. We think that cytokines and the formation abnormality of collagen fibers are related to the production of aneurysms.

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**Keywords:** Cytokine; Mycotic aneurysm; Bacterial endocarditis; Down's syndrome

### 1. Introduction

Cerebral mycotic aneurysms are one of the most serious complications of bacterial endocarditis and there has been a report of one in a child with Down's syndrome [1]. The mechanism underlying cerebral aneurysms is unclear. Cytokines are important mediators of abdominal aortic aneurysms [2] and coronary aneurysms of Kawasaki disease [3]. We reported the cytokine levels in a cerebral mycotic aneurysm in a child with Down's syndrome.

### 2. Case report

The patient was a 12-year-old female. She was diagnosed as having Down's syndrome and congenital heart disease consisting of an endocardial cushion defect at birth. She underwent a radical operation at the age of 9 years but mitral valve regurgitation remained. She had been admitted to our hospital previously on 22 August 2001 because of infarction of the middle cerebral artery on the left side with bacterial endocarditis. She was hospitalized on 25 January 2002 with high fever, vomiting, loss of activity and gait disturbance. On admission, she was crying with displeasure. Neurological examination revealed facial palsy and hemiparesis on the left side. She could not stand. Sense of pain in the upper and lower limbs on the left side was present. Cerebellar and extrapyramidal signs were not observed. Routine laboratory tests revealed the following: white blood cells, 18,600/mm<sup>3</sup> (reference = 4000–8000); platelets, 177,000/mm<sup>3</sup> (reference = 150,000–300,000); C-reactive protein, 7.1 mg/dl

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(reference <0.1) and ferritin, 197  $\mu\text{g}/\text{dl}$  (reference = 2–128). The level of ferritin decreased at 167  $\mu\text{g}/\text{dl}$  2 days later. Blood coagulation values including the partial thromboplastin time, activated partial thromboplastin time, protein S and protein C were all within normal range. Antiphospholipid antibodies were negative. Cerebrospinal fluid (CSF) analysis revealed pleocytosis (1867/ $\text{mm}^3$ , 49% polymorphs and 51% lymphocytes), 218 mg/dl protein and 49 mg/dl glucose. Herpes simplex antibodies were not elevated. The beta 2 microglobulin levels in blood and urine were 2.3 mg/l (reference = 0.8–1.8) and 7390  $\mu\text{g}/\text{dl}$  (reference <200). Two days later, beta 2 microglobulin levels of urine was 931  $\mu\text{g}/\text{dl}$ . The interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), soluble TNF receptor 1 (sTNFR1), and soluble E selectin (sE-selectin) levels in blood were 107 pg/ml (reference <3.1), 27.6 pg/ml (reference <4.4), 5.07 ng/ml (reference = 0.55–1.33), and 284 ng/ml (reference = 40–60), respectively. The IL-6, TNF- $\alpha$  and sTNFR1 levels in CSF were 6059 pg/ml (reference <3.1), 83.4 pg/ml (reference <4.4), and 3.13 ng/ml, respectively. Staphylococcus aureus was detected in cultures of the pharynx swab. Blood, stool and CSF cultures were negative. Mitral valve regurgitation and vegetation were detected on echocardiography. Computed tomography (CT) disclosed edema of the right cerebrum, and high density of the Sylvian sulcus and suprasellar cistern on the right side and in the longitudinal cerebral fissure (Fig. 1). We considered it as cerebral bleeding.

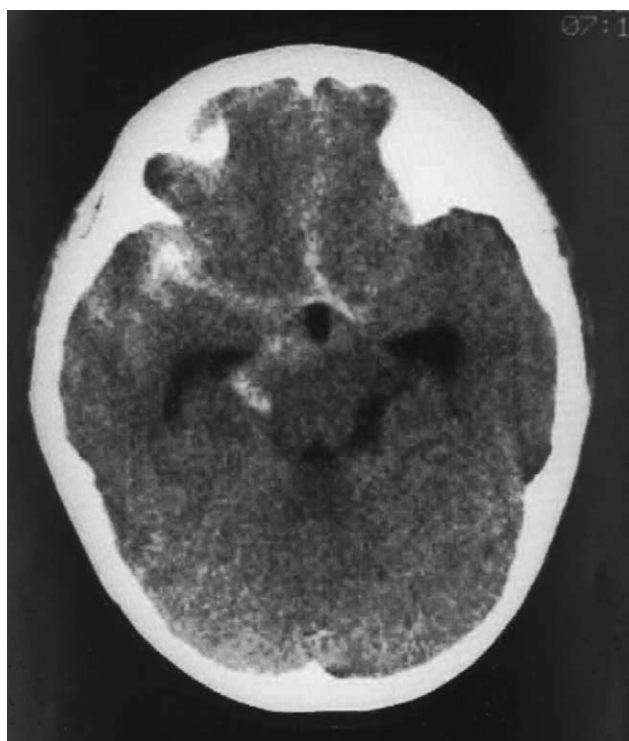


Fig. 1. Computed tomography disclosed edema of the right cerebrum, and high density of the Sylvian sulcus and suprasellar cistern on the right side and in the longitudinal cerebral fissure. We considered it cerebral bleeding.

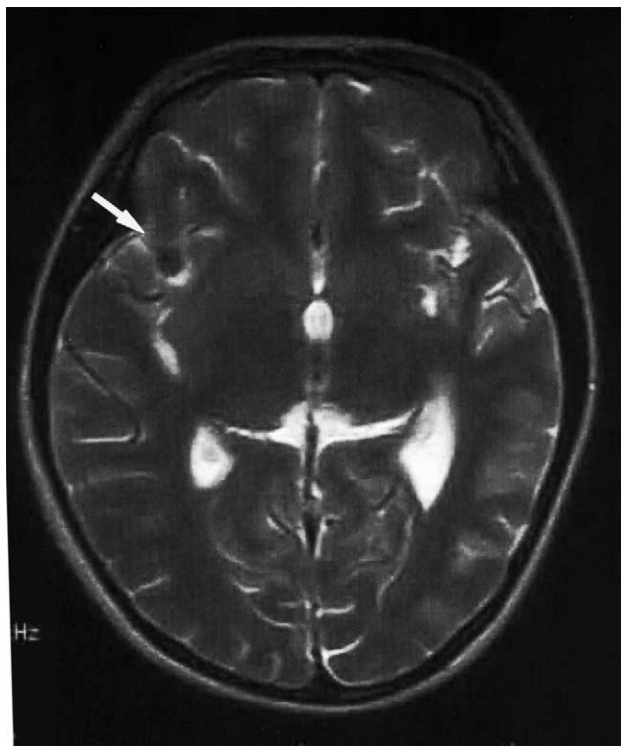


Fig. 2. T2-weighted MRI disclosed a low intensity area in the right Sylvian sulcus (arrow).

T2-weighted MRI disclosed a low intensity area in the right Sylvian sulcus (Fig. 2). MR angiography (MRA) showed an aneurysm of the right middle cerebral artery (Fig. 3). The aneurysm had not been seen 5 months ago. The patient was treated with ampicillin, cefotaxm and glycerol. The antibiotics was changed to cefotiam, which was administered for 4 weeks. Six weeks later, MRA disclosed embolization of the aneurysm. So she did not undergo surgical intervention. Repeated echocardiography disclosed moderate residual mitral regurgitation. She was discharged 6 weeks later. She could walk but bilateral palsy remained.



Fig. 3. MR angiography showed an aneurysm of the right middle cerebral artery (arrow).

### 3. Discussion

Cerebral mycotic aneurysms in bacterial endocarditis with childhood have been reported in Down's syndrome and Ehlers–Danlos syndrome [1,4]. The mechanism underlying cerebral aneurysms is unknown. The pathogenesis of abdominal aortic aneurysms is a complex process in which arterosclerosis and inflammation play leading roles. Cytokines are important mediators of both processes. The plasma concentrations of cytokines are higher in abdominal aortic aneurysm patients [2]. In Kawasaki disease, cytokines play important roles in the pathogenesis of both the immune dysfunction and the endothelial cell damage characteristic of coronary aneurysms. The highest serum levels of IL-6 and IL-8 are found in the first week after the onset of disease, and the levels observed in the first week are highly correlated with those of other acute phase reactants [3]. Regarding histological findings, endothelial swelling, necrosis, macrophage and activated T cell infiltration, and fibrin deposition are observed in endothelial lesions [5]. Leung et al. hypothesized that the endothelial cell damage occurs through two immunological steps [6]. First, elevated cytokines produced by the activated immune system induce endothelial cells to express adhesion molecules. This results in the infiltration of mononuclear cells into the endothelium. Endothelial cells are also induced to express a new antigen. Second, a cytotoxic antibody toward the new antigen is produced. The already activated immune system may support the production of this cytotoxic antibody. These two steps comprise the initial stage of endothelial cell injury.

Intracranial production of cytokines has been demonstrated after acute disseminated encephalomyelitis [7] and encephalopathy [8]. The CSF IL-6, IL-10, TNF- $\alpha$ , and sTNFR1 concentration were elevated in 16, 13, 3, and 11 of the 18 patients with acute disseminated encephalomyelitis, respectively. Myelin basic protein levels in CSF of the patients with elevated CSF sTNFR1 levels were significantly higher than those in CSF of the patients with normal CSF sTNFR1 levels. So they suggested that IL-6 and TNF- $\alpha$  were mediate inflammation in the central nervous system in acute disseminated encephalomyelitis [7]. And cytokines and sTNFR1 in serum and CSF were elevated with influenza virus-associated encephalopathy, and that the CSF TNF- $\alpha$  and sTNFR1 levels may be important for predicting neurological sequelae [8]. In our case, cytokines such as IL-6, TNF- $\alpha$ , sTNFR1 and sE-selectin were elevated in blood, and IL-6, TNF- $\alpha$  and sTNFR1 in CSF. IL-6 and TNF- $\alpha$  are well known as cytokines that play important roles in inflammatory responses. These cytokines are recognized as primary mediators in the pathogenesis of inflammation. The concentrations of IL-6, TNF- $\alpha$  and sTNFR1 are often elevated in the CSF of patients with infectious inflammatory disorders [7]. sE-selectin is an endothelial-specific surface protein.

Adhesion molecules such as sE-selectin are primarily found in a soluble form after endothelial cell activation and leukocyte–endothelial cell interaction [8]. In MRA, an aneurysm of the right cerebral artery appears in the acute phase. The aneurysms in our case was not seen 5 months ago. The distribution of collagen type VI is different from normal in the skin in trisomy 21, and there is overexpression of COL6A1 [9]. In Down's syndrome with the moyamoya abnormality, there were occlusions or stenosis in arteries due to fibrous hypertrophy of the arterial intimal walls. The tunica media was highly atrophic and the internal elastic lamina was tortuous and duplicate [10,11]. So we think that cytokines and the formation abnormality of arteries are related to the production of aneurysms.

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