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Soluble adhesion molecules in Gilles de la Tourette's syndrome

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Abstract

To investigate the immune-mediated response in TS, and its relationship with streptococcal infection, we measured serum levels of soluble intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin in patients with TS, compared to healthy and diseased controls. Soluble VCAM-1 and sE-selectin were significantly elevated in children and adults with TS, and sVCAM-1 was higher among anti-basal ganglia antibodies (ABGA)-positive adults with TS. No correlation of adhesion molecule levels to clinical severity or anti-streptococcal antibodies was observed. Children with Sydenham's chorea and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) showed an increased level of sICAM-1, but not sVCAM-1 and sE-selectin. These results provide initial evidence for a role of adhesion molecules and systemic inflammation in TS, and support the hypothesis of an ongoing immune-mediated process in this condition.

Keywords: Tourette's syndrome; sICAM-1; sVCAM-1; sE-selectin; Adhesion molecules; Streptococcal infection; Anti-basal ganglia antibodies

1. Introduction

Gilles de la Tourette's syndrome (TS) is characterised by the presence of multiple chronic motor and phonic tics [1]. The aetiology of TS is still undefined, although several different genetic and environmental factors might play a role [2–5]. A relationship between the occurrence of tic disorders and Group A β-hemolytic streptococcal (GABHS) infections has been proposed [4] and intensely debated [6–8], leading to the description of the PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) syndrome [9]. Interestingly, PANDAS show similarities to TS, mainly the predominance of tics in both syndromes, a high frequency of psychiatric comorbidity, such as obsessive–compulsive disorder (OCD) and anxiety disorders, and the waxing and waning of symptoms [1,9,10].

On the model of Sydenham's chorea (SC), a neuropsychiatric disorder related to rheumatic fever (RF), PANDAS are hypothesized to be an autoaggressive disorder triggered by molecular mimicry between surface GABHS antigens and neuronal antigens, enriched in the basal ganglia [11,12]. Cross-reacting autoantibodies were proposed to play a role in this process [11,13], and serum anti-basal ganglia antibodies (ABGA) were suggested as a potential diagnostic marker in post-streptococcal neurological and psychiatric disorders [14,15].

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Several reports showed elevated titers of anti-streptococcal antibodies in TS [16–18], and a cross-sectional study reported a higher frequency of ABGA in the serum of 100 patients with TS, compared to healthy and diseased controls [18]. This preliminary evidence led to the hypothesis that autoimmunity directed against the basal ganglia, triggered by GABHS infection, is involved in a subgroup of patients with TS. However, reports on markers related to systemic autoimmune diseases have been rare in TS.

Cellular adhesion molecules (intercellular adhesion molecule-1, ICAM-1; vascular cell adhesion molecule-1, VCAM-1; selectins) are glycoproteins belonging to the immunoglobulin superfamily, which mediate cell–cell and cell–extracellular matrix interactions [19]. Their expression is increased in a large number of inflammatory and immune-mediated conditions, including multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) [20]. When expressed by endothelial cells in their membrane-bound form, these molecules act as ligands for leukocytes to facilitate their entry into the sites of inflammation [19]. Serum levels of soluble ICAM-1 are raised also in patients with RF, and such increase is maintained over time, until clinical remission [21].

To explore the concurrence of an immune-mediated inflammatory response in TS, we measured serum levels of the soluble forms of three adhesion molecules in children and adults with TS, and analysed their relationship to serological markers of recent streptococcal infection and the presence of ABGA.

2. Materials and methods

2.1. Subjects

Permission for the study was obtained from the ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Thirty-three children and 51 adults diagnosed with TS were consecutively recruited from a tertiary referral centre of the same institution. Patients diagnosed with TS fulfilled DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 1992) criteria, and were not preselected on the basis of a preceding streptococcal infection. Diagnostic interviews were performed by two specialists in TS (MO and MMR), using standardised instruments, including the National Hospital interview schedule [22], the Diagnostic Confidence Index (DCI) [23] and the Yale global tic severity rating scale (YGTSS) [24].

To determine the significance of serum levels of soluble ICAM-1 (sICAM-1), soluble VCAM-1 (sVCAM-1) and soluble E-selectin (sE-selectin), we studied several controls for comparison:

Children with non-inflammatory neurological diseases (NNID, $n=35$). This group contained 10 children with developmental delay, 14 children with epilepsy and 11 children with diagnosed CNS metabolic disorders.

Healthy children ($n=34$).

Children with post-streptococcal neuropsychiatric diseases (SC or PANDAS, $n=19$). Nine patients were diagnosed with acute SC: they all presented with an acute onset of chorea, met the modified Jones criteria for RF [25], and other causes of chorea were excluded. Ten patients fulfilled the working criteria for PANDAS [9]. All children in this group entered the study within 2 weeks from the onset of the acute illness.

Adults with non-inflammatory neurological diseases (NNID, $n=40$). This group contained 28 patients with primary adult-onset dystonia, 7 patients with primary hemifacial spasm, 3 patients with dopa-responsive dystonia, 1 with paroxysmal kinesigenic choreoathetosis and 1 with DYT-1 dystonia.

Healthy adults ($n=30$).

Subjects with NNID and children with SC or PANDAS were consecutively recruited from other tertiary referral centres of the same institution. Healthy controls were recruited from laboratory staff and hospital workers, and from their relatives. Diseased and healthy controls were matched to TS patients by age (±5 years), recruiting each suitable subject in a consecutive fashion. No subject, other than SC/PANDAS patients, had had RF, SC or an autoimmune disease. Case or control subjects affected by a clinically evident infectious or inflammatory disorder at the time of recruitment were excluded from the study. All subjects were recruited during the same period. A blood sample was taken from each subject, and aliquots of serum specimens were frozen within 30 min of collection and stored at −80 °C with identification data coded until analysis.

2.2. Adhesion molecules

Soluble adhesion molecules (sICAM-1, sVCAM-1 and sE-selectin) were quantified from patient sera using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) (R&D Systems Europe, Abingdon, Oxon, UK), following the protocol of the manufacturer. A monoclonal antibody specific for sICAM-1 had been pre-coated onto a 96 well microplate. Antibody to recombinant human sICAM-1 conjugated to horseradish peroxidase was then added to the wells. Standards, positive controls and sera were then incubated for 90 min at room temperature, at a 1:20 dilution. After washing, a colorimetric reading of the microplate by measurement of the absorbance at 450 nm was performed, using a tetramethylbenzidine solution as substrate. The same protocol was used for sVCAM-1 and sE-selectin quantitative measurements, using a 1:50 dilution for sVCAM-1 and a 1:20 dilution for sE-selectin.

2.3. Streptococcal serology

Evidence of recent streptococcal infection was examined using antistreptolysin O (ASOT) and anti-DNAse B titers.