Elevated CSF histamine levels in multiple sclerosis patients

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Abstract: BACKGROUND: Histamine is an ubiquitous inflammatory mediator of numerous physiological processes. Histamine and its receptors have been implicated in multiple sclerosis (MS) disease pathogenesis. We prospectively enrolled 36 MS patients and 19 age and gender-matched healthy volunteers for cerebrospinal fluid (CSF) histamine analysis. FINDINGS: CSF histamine levels in MS patient samples were significantly higher (median: 35.6 pg/ml) than in controls (median: 5.5 pg/ml; Beta = 0.525, p < 0.001). In addition, histamine increased with age (Pearson's correlation, p < 0.003). CONCLUSIONS: Histamine may be an important factor for both the initiation and maintenance of chronic inflammatory diseases of the central nervous system. Our observation encourages a deeper investigation of the role of histamine in MS.

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Elevated CSF Histamine Levels in Multiple Sclerosis Patients

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Introduction

Multiple sclerosis (MS) is a complex autoimmune disease with inflammation and demyelination within the central nervous system (CNS). Histamine and its receptors have been implicated in MS disease pathogenesis. Histamine is an ubiquitous inflammatory mediator of numerous physiological processes including local immune responses and allergic reactions, and it plays an important role in neurotransmission. The functions of histamine are mediated through 4 G-protein coupled receptors (H1-H4 receptors). Histamine and histamine receptors play a regulatory role in experimental allergic encephalomyelitis (EAE), the animal model of MS [1-3]. Rodent experiments revealed that histamine increases the permeability of the blood brain barrier, promoting CNS inflammation [3-5]. The cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) in auto-reactive T helper cells is mandatory to induce and sustain EAE in mice [6]. GM-CSF stimulates granulocytes and macrophages, and both secrete histamine. A small study by Tuomisto et al., 1983 [7] reported on higher CSF histamine level by about 60% both in patients with remitting and progressive type of MS than in controls. Based on this observation and previous studies in EAE, we hypothesized that histamine might play a role in MS. Thus, we aimed at testing whether histamine is elevated in the CSF of MS patients.

Methods

We prospectively enrolled consecutive MS patients of Caucasian origin treated in the MS center of the University Hospital Zurich and age and gender-matched healthy volunteers. In all patients, the diagnosis of MS was made according to the current criteria. We enrolled all types of MS. In all patients, a diagnostic lumbar puncture was performed. In the controls, cerebrospinal fluid (CSF) was ascertained during spinal anesthesia. Subjects with signs of neurological or sleep-wake disorders were not included as controls. All patients and healthy controls gave informed written consent. This study was approved by the local ethics committee.
After assessment of CSF, samples were immediately put on dry ice and stored at -80°C. Samples were separated by high-performance liquid chromatography (HPLC), thereafter histamine was post-labeled by O-phthalaldehyde and detected by fluorometric analysis. [8] HPLC has been used for the measurement of histamine in CSF in other neurological disorders. [9] Statistical analyses were performed with SPSS 19.0. Group data are described by means and standard deviations (SD). For the comparison of parametric data, we Student’s t-tests, and for non-parametric data, Whitney U-test was used. For correlation analyses in parametric data, we used a two way Pearson analysis. To control for effects of sex, age and different types of MS on histamine concentrations, we ran multivariate nominal regression analyses.

Results

We included 36 MS patients (51±10 years; 64% female; 24 patients with secondary progressive disease, 12 relapsing-remitting) and 19 healthy volunteers (46±10 years, 37% female). CSF histamine levels in patient samples were significantly higher (36.5±30.8 pg/ml) than in controls (12.0±18.6; Wald=5.7; p=0.017). In addition, histamine increased with age (Pearson's correlation, p=0.003), but were similar men (30.0 ± 27.0) and women (39.2 ± 6.4; t = 0.89; p = 0.381) and were not associated with diagnosis of relapsing remitting (26.0 ± 28.2) versus secondary progressive MS (39.9 ± 31.6; t = 1.5; p = 0.154).

Discussion

This study confirmed results by Tuomisto et al. [7] and our hypothesis that histamine levels are increased in MS patients The GM-CSF mediated stimulation of granulocytes and macrophages may be one possible underlying mechanism. Thus histamine may be an important factor for both the initiation and maintenance of chronic inflammatory diseases of the central nervous system such as multiple sclerosis (MS). Our results are limited by the small study size and the large intra-group variability of histamine levels. However, this observation encourages a deeper investigation
of the role of GM-CSF, granulocytes, macrophages and histamine in MS. Further, histamine may be investigated as diagnostic marker for MS and other inflammatory CNS diseases.
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Cerebrospinal fluid histamine levels in 36 patients with multiple sclerosis and in 19 healthy controls. Each dot represents one patient, and horizontal lines depict mean levels per group.