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Rasmussen's encephalitis and Behcet's disease: autoimmune disorders in first degree relatives

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ABSTRACT – We report a patient with adolescent-onset, Rasmussen's encephalitis, presenting with intractable focal seizures, mild hemiparesis, cognitive impairment, dystonia, and severe hemiballism. His father had Behcet's disease, considered to be an autoimmune disorder. Recent reports have directly implicated the role of cytotoxic T lymphocytes in the pathogenesis of both Rasmussen's encephalitis and Behcet's disease. The occurrence of Behcet's disease and Rasmussen's encephalitis in the same family suggests involvement of common genetic factors such as HLA haplotypes in both autoimmune disorders. It is possible that members of this family are genetically susceptible to developing autoimmune conditions that have been precipitated by separate environmental triggers.

Key words: Rasmussen's encephalitis, Behcet's disease, hemiballism, autoimmune disorder

Rasmussen's encephalitis (RE) is a chronic inflammatory disease of unknown origin usually affecting one brain hemisphere (Rasmussen *et al.* 1958), it is characterized by intractable focal epilepsy, often epilepsia partialis continua (EPC), associated with progressive hemiparesis, cognitive impairment, and progressive unilateral cerebral atrophy (Hart 2004, Hart and Andermann 2000). Since the original description, a number of atypical features have been described. The disorder usually affects children, although adolescent- and adult-onset RE have been recognized (McLachlan *et al.* 1993, Hart *et al.* 1997). More recently, movement disorders, such as chorea, athetosis, or dystonia, have been reported at the onset (Bhatjiwale *et al.* 1998, Frucht 2002).

Rasmussen *et al.* in their orginal description, assumed a viral cause for the disease (Rasmussen *et al.* 1958). In recent years however, attention has shifted towards the role of humoral factors, namely autoantibodies, as well as autoimmune, cytotoxic T lymphocytes in the pathogenesis (Bien *et al.* 2005).

We report a patient with adolescent-onset RE, presenting with intractable focal seizures, mild hemiparesis, cognitive impairment, dystonia, and se-

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vere hemiballism. MRIs showed progressive hemiatrophy, starting in the basal ganglia and the fronto-insular region and subsequently spreading to involve the rest of the hemisphere. His father had Behcet's disease (BD), considered to be an autoimmune disorder (Direskeneli 2006).

Case history

A 17-year-old, right-handed boy had a three-year history of focal and generalized seizures. He was the result of a normal pregnancy and delivery. His father had Behcet's disease. He was healthy until age 14 years, when he experienced his first seizure with twitching of the left face, and head-turning to the left followed by secondary generalization during sleep. A few months earlier, he was hit by a ball and briefly lost consciousness. Four months later he had a second attack followed by frequent, secondarily generalized tonic clonic seizures. He was treated with valproic acid and phenobarbital with only partial success. Seven months later, he developed involuntary throwing and flinging movements of the left arm and leg, and intermittent prolonged twisting and posturing movements of the left hand and forearm. His left ankle began to invert when he walked. Valproic acid was changed to carbamazepine, and despite a brief trial of haloperidol, his involuntary movements did not improve. After haloperidol was changed to clonidin, the ipsilateral, ballistic movements gradually regressed over one year.

He complained that his left side was numb and no longer as strong as his right side. These symptoms stabilized over the past two years. He developed complex partial seizures with absence, lipsmacking, deviation of the head to the left, twitching of the left side of the face and sometimes clonic movements of the left arm, several times daily. Despite treatment with carbamazepine, phenobarbital, and topiramate in combination, his seizures remained refractory to treatment.

Neurological examination showed mildly increased tone and 4+/5 weakness in the left leg, a pronator drift, left-sided hyperreflexia, and a Babinski sign. At rest and particulary when he walked, his left foot inverted and assumed a dystonic posture. Neuropsychological assessment revealed mild impairment in word finding, articulation and in verbal working memory. Cerebrospinal fluid analysis, DNA analysis for Huntington's disease, DRPLA, and mitochondrial analysis, serum lactate, pyruvate, copper, ceruloplasmin, blood and urine screening for inborn errors of metabolism, thyroid function studies, arylsulfatase, hexosaminidase, sedimentation rate, antiphospholipid antibodies, and antinuclear panel were unremarkable. EEG showed focal slowing in the right frontotemporal region and bilateral fronto-central spiking. Four months after the appearance of symptoms, the first MRI showed a hyperintense signal over the right fronto-insular region, the right caudate, and putamen with mild atrophy of the caudate and lentiform nuclei *(figure 1A, B)*. One year later, MRI demostrated progression with enlargement of the sylvian fissure, mild enlargement of the lateral ventricle, atrophy, and hyperintensity in the caudate head and putamen *(figure 1C, D)*. Three years later, a third MRI showed progressive atrophy of the affected hemisphere *(figure 1E, F)*. An 18-fluoro-deoxy-glucose PET scan showed hypometabolism in areas atrophic on MRI, no areas of hypermetabolism, and normal metabolic activity in the left hemisphere *(figure 2)*. There was no reduction in seizure frequency following treatment with IVIg.

He remanined stable over one year, with no change in seizure frequency, neurological examination or neuropsychological performance.

A diagnosis of RE was based on previously reported diagnostic criteria (Hart *et al.* 1997) and the recently proposed European consensus statement (Bien *et al.* 2005). Given the mildness of his hemiparesis, and in accordance with his wishes, hemispherectomy has not been performed.

Discussion

Rasmussen's encephalitis typically begins in childhood; however, adolescent- and adult-onset forms have been described by several groups (McLachlan *et al.* 1993, Hart *et al.* 1997). These may mimic the early-onset form, but usually have a milder clinical course with less residual functional deficit. A more frequent involvement of the occipital lobe has been reported in adolescents and adults. Movement disorders were initially underreported but recent studies have focused on athetosis, dystonia, or choreic movements correlating with selective frontal cortical and caudate athropy (Frucht 2002). They typically start at onset or early in the course of the disease.

A humoral or cellular autoimmune process is assumed to be responsible for both the intractable epilepsy and the involuntary movements (Frucht 2002). A head injury or other insult has often been recalled to precede the illness, although this remains an unproven etiological link. Glutamate receptor GluR3 autoantibodies have been found in some, but not all patients with RE, supporting an autoimmune etiology (Mantegazza *et al.* 2002). The disease might be initiated by a focal insult such as a head injury, infection or repeated seizures, leading to breakdown of the blood brain barrier and initiation of an immune-mediated cascade of tissue injury, leading to further seizures and further breakdown of the blood brain barier (Antel and Rasmussen 1996, Hart and Andermann, 2000).

Finally, the occurrence of Behcet's disease and RE in the same family (father and son) suggests involvement of common genetic factors such as HLA haplotypes in both diseases. This assumption is supported by RE patients with uveitis, which is frequently observed in Behcet's disease (Gray *et al.* 1987, Harvey *et al.* 1992, Fukuda *et al.* 1994).

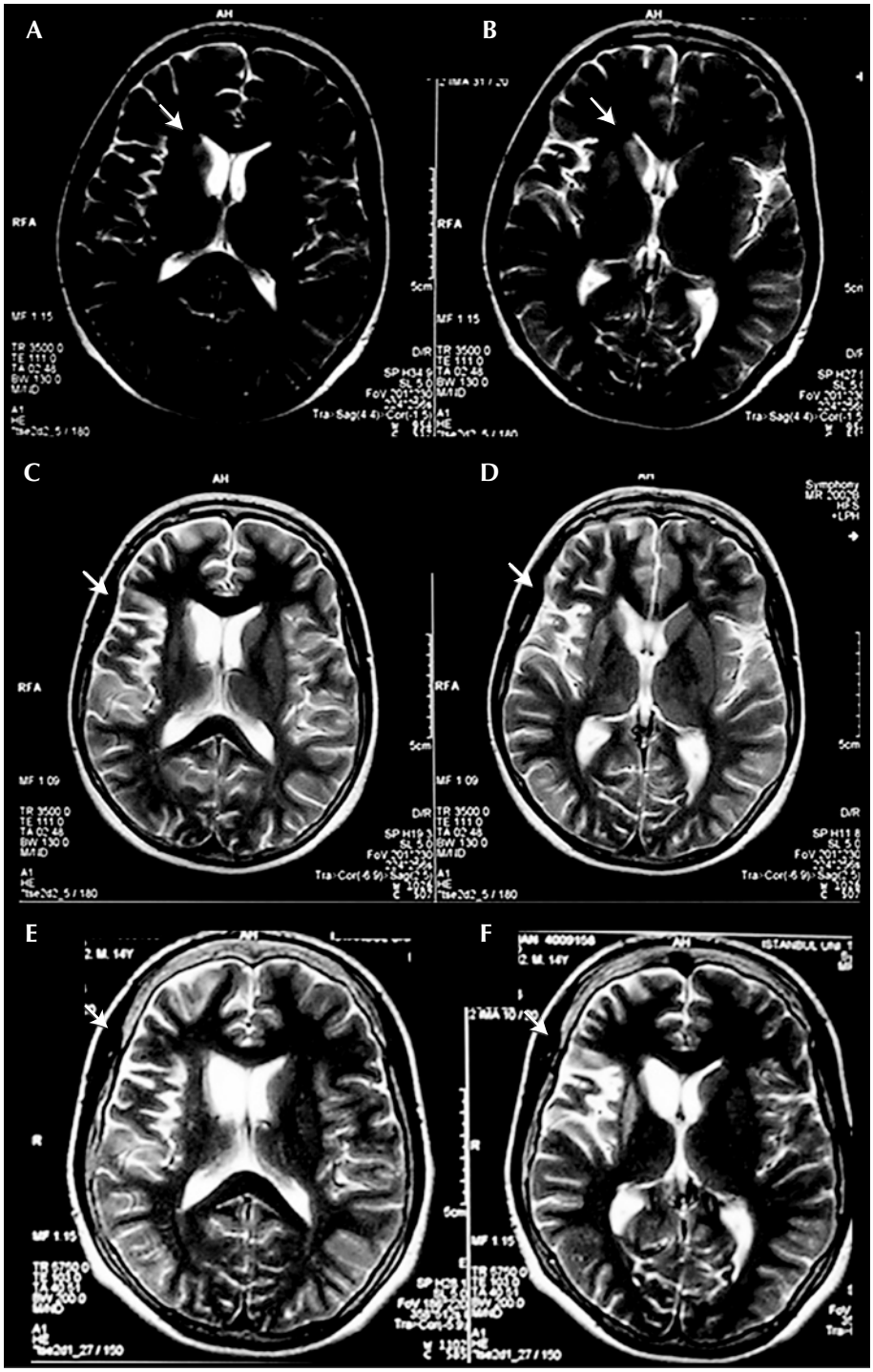

Figure 1. Axial T2-weighted images taken four months (**A, B**), one year (**C, D**), and three years (**E, F**) after the first seizure. In **A** and **B**, a hyperintense signal over the right fronto-insular region, the right caudate, and putamen with the beginnings of atrophy of the right caudate and lentiform nucleus is evident. Later images (**C, D**) show progression, with enlargement of the sylvian fissure, mild enlargement of the lateral ventricle, atrophy and hyperintensity in the caudate head and putamen. Three years later (**E, F**), progressive atrophy of the affected hemisphere was seen.

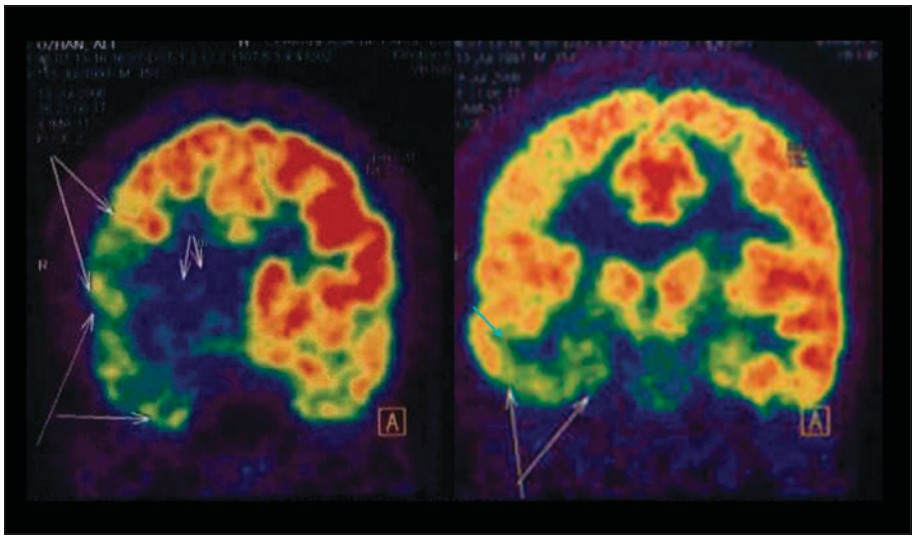

Figure 2. An 18-fluoro-deoxy-glucose PET scan showed hypometabolism in areas atrophic on MRI.

The occurence of uveitis prior to or in the early stages of the disease in a few patients with typical RE (Gray *et al.* 1987, Harvey *et al.* 1992, Fukuda *et al.* 1994), has led to speculation that an underlying viral etiology may be responsible for both. Although a viral etiology was suggested by Rasmussen based on pathological findings in the brain such as lymphocyte infiltration and microglial nodules (Rasmussen 1958), the occurence of a preceding infectious or inflammatory event in about 50% of patients, and the similarities with Russian spring-summer tick-borne encephalitis (Hart and Andermann 2000), attempts to identify a pathogenic viral agent have been contradictory or inconclusive (Bien *et al.* 2005). In the absence of a clearly demonstrable infectious pathogen, RE is regarded as an autoimmune disorder (Aarli 2000). Evidence is accumulating which suggests the role of B and cytotoxic T lymphocytes in the pathogenesis (Bien *et al.* 2005). The range of abnormalities found on pathology examination indicates that RE may be a single clinical entity occurring as a result of a variety of pathophysiological mechanisms (Hart *et al.* 1998).

Behcet's disease (BD) is an inflammatory disorder characterized by uveitis, oral and genital aphthous ulcers, and skin lesions (Sakane *et al.* 1999). The geographic distribution of BD, with its high-prevalence from southern Europe to Japan along the Silk Route, the susceptibility strongly associated with HLA-B51 and microbial infection, and a strong genetic background with familial aggregation, indicate that both genetic and environmental factors contribute to the pathogenic process of BD (Gul *et al.* 2000, Ohno *et al.* 1982). Evidence for linkage of the HLA-B locus in BD has also recently been shown (Gul *et al.* 2001).

Sibling recurrence rate-defined as the ratio of the risk of being affected among the siblings of patients and the risk of being affected in the general population - was found to be 4.2% for Behcet's disease (95% CI 1.2 to 7.2%) and 13.3% for recurrent oral ulcers (95% CI 8.1 to 18.5%), which gives a λs value for Behcet's disease in Turkey, of between 11.4 and 52.5 (Gul *et al.* 2000). To calculate λs in Turkey, the data from previous studies, giving a point prevalence rate of 8-37/10 000 for BD (Idil *et al.* 2002, Tuzun *et al.* 1996), were used. Shared environmental factors alone are unlikely to account for such a high λs value. These findings provide strong evidence for an hereditary background in BD.

Recent reports have directly implicated the role of cytotoxic T lymphocytes in the pathogenesis of both RE and BD. Although the nature of the antigen that may trigger such a response is unknown, an antigen-driven, oligoclonal increase of T cells has been observed in both (Li *et al.* 1997, Direskeneli *et al.* 1999). On the other hand, stress proteins, autoantigens, or a pathogen may provoke a chronic, autoimmune response (Bauer *et al.* 2002, Direskeneli 2006). Yasuoka *et al.* (2004), were the first to report on BD characterized by an increase in autoreactive, cytotoxic T lymphocytes directed at a transmembrane peptide of the stress-inducible antigen, major histocompatibility complex class I chain-related gene A (MIC-A) expressed on epithelium and endothelium and presented to autoreactive cytotoxic T lymphocytes in the contex of HLA-B51. Another group found that the aqueous humor from Behcet's uveitis was characterized by the predominant presence of activated CD8+ T lymphocytes (Yu *et al.* 2004) and more generally, peripheral blood CD8+ T lymphocytes are found to exhibit an activated phenotype in patients with active Behcet's (Houman *et al.* 2004). Immunohistochemical studies on RE brain specimens have provided evidence of granzyme B-mediated cytotoxic T lymphocyte attacks against neurons (Bien *et al.* 2002). T cells containing granzyme B-positive granules, target cells

(in this case neurons) expressing major histocompatibility complex class I, and neurons in these lesions that were apoptotic have been documented in RE.

Autoimmune disorders constitute a diverse group of phenotypes, with overlapping features and a tendency toward familial aggregation. The occurence of common features of autoimmune diseases and the co-association of multiple autoimmune diseases in the same individual or family suggests shared genetic predisposition for these clinically related diseases (Becker, 2001). Shared autoimmunity may occur within families, not only in multiplex families with several members having the same autoimmune disease, but also families with members afflicted by various autoimmune disease. In a recent study of a large number of Latin American, systemic lupus erythematosus (SLE) patients participating in the GLADEL cohort, Alarcón-Segovia *et al.* (2005), found familial aggregation, not only of SLE, but also of rheumatoid arthritis (RA), autoimmune thyroid disease and autoimmune diseases in general. The multiple autoimmune disease genetics consortium (MADGC) collection of families was originally conceived to be a resource for identifying the common genetic elements involved in autoimmunity, and was based on the idea that certain alleles may act to predispose to several different autoimmune diseases (Criswell *et al.* 2005). They have described a unique registry of 265 multiplex families that have been specifically identified as having two or more different autoimmune diseases within the same family. At least two of the nine core diseases, including rheumatoid arthritis, SLE, type 1 diabetes, multiple sclerosis (MS), autoimmune thyroid disease (Hashimoto's thyroiditis or Graves' disease), juvenile rheumatoid arthritis, inflammatory bowel disease, psoriasis, and primary Sjögren syndrome have occurred in each of these families. They showed that a relatively common variant of PTPN22, 620 W, confers susceptibility to four different autoimmune disorders: type 1 diabetes, rheumatoid arthritis, SLE, and Hashimoto's thyroiditis. MS did not show an asociation with the PTPN22 risk allele.

The occurrence of two autoimmune disorders such as BD and RE in first degree relatives has not been previously described. This may be a significant association even when considering the relatively high frequency of BD in the Turkish population. It is possible that patients are genetically susceptible to developing autoimmune conditions that have been precipitated by separate environmental triggers. □

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