Mitochondrial carrier homolog 1 (Mtch1) antibodies in neuro-Behçet's disease

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1. Introduction

Behçet’s disease (BD) is a chronic, recurrent and inflammatory disorder characterized with oral and genital aphthous ulcerations, uveitis, skin lesions and skin pathergy reaction (Gül, 2005; Yurdakul and Yazici, 2008). The presence of inflammatory lesions in involved tissues, increased levels of cytokines and acute phase reactants and identification of autoantibodies [directed against heat shock proteins (HSP)-60, -65 and -70, αB-crystallin, stress-induced-phosphoprotein 1, PTEN-related protein, as a potential autoantigen. ELISA studies showed serum Mtch1 antibodies in 68 of 144 BD patients with or without neurological involvement and in 4 of 168 controls corresponding to a sensitivity of 47.2% and specificity of 97.6%. Mtch1 antibody positive BD patients had more attacks, increased disability and lower serum nucleosome levels. Mtch1 antibody might be involved in pathogenic mechanisms of BD rather than being a coincidental byproduct of autoinflammation.

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Abstract

Efforts for the identification of diagnostic autoantibodies for neuro-Behçet’s disease (NBD) have failed. Screening of NBD patients’ sera with protein macroarray identified mitochondrial carrier homolog 1 (Mtch1), an apoptosis-related protein, as a potential autoantigen. ELISA studies showed serum Mtch1 antibodies in 68 of 144 BD patients with or without neurological involvement and in 4 of 168 controls corresponding to a sensitivity of 47.2% and specificity of 97.6%. Mtch1 antibody positive BD patients had more attacks, increased disability and lower serum nucleosome levels. Mtch1 antibody might be involved in pathogenic mechanisms of BD rather than being a coincidental byproduct of autoinflammation.

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2. Materials and methods

2.1. Patients and samples

Thirty-two consecutive NBD patients (13 women, 19 men; mean age ± standard error, 36.4 ± 1.7) were included. The average NBD duration (± standard error) of these patients was 9.9 ± 1.3 years. Age- and gender-matched controls included 112 BD patients without neurological involvement (41 women, 71 men; mean age, 37.3 ± 1.6; disease duration 9.6 ± 2.3), 47 patients with relapsing remitting multiple sclerosis (25 women, 22 men; mean age, 34.3 ± 1.1; disease duration 9.6 ± 2.1), 21 neuromyelitis optica (NMO) patients (12 women, 9 men; mean age, 32.6 ± 1.5; disease duration 8.7 ± 1.3) and 100 healthy controls (47 women, 53 men; mean age, 35.7 ± 1.9). There were no statistically significant differences between NMO patients and control groups by means of age, gender and disease duration (p > 0.05 by Fisher’s exact test or Student’s t-test). None of the patients had a history of a concomitant neurological disease. NBD and BD patients fulfilled the diagnostic criteria for BD (International Study Group for Behçet’s Disease, 1990), MS patients fulfilled McDonald’s criteria for definite MS (Polman et al., 2005) and NMO patients fulfilled the revised Wingerchuk criteria (Wingerchuk et al., 2006). EDSS scores of NBD patients were calculated during serum sampling. An informed consent was obtained from all participants before blood samples were obtained. Sera were kept frozen at −80 °C until assayed. Blood samples were collected from all NBD and BD patients prior to the initiation of steroid treatment, especially when the sample was obtained during an attack. However, the interference of immunosuppressive therapy with antibody levels could not be completely avoided. While all NBD patients were under long term azathioprine treatment when sera were collected, 58 BD patients were under immunosuppressive treatment and 54 BD patients were not receiving any immunosuppressants. The study was approved by the Ethics Committee of Istanbul Faculty of Medicine of Istanbul University.

2.2. Protein macroarray, sequencing of cDNA inserts and protein expression

To identify NBD related anti-neuronal antibodies, pooled sera of 10 randomly selected NBD patients were screened using a high-density protein macroarray derived from human fetal brain cDNA expression library, which contains approximately 24,000 clones (ImaGenes, Berlin, Germany) (Preuss et al., 2009). Images were captured and analyzed for signal intensity (VisualGrid, GPC Biotech, Martinsried, Germany). The arrays were scored as 0 (absent), 1 (weak), 2 (moderate) and 3 (strong) confirmed by matched duplicates. Selected expression clones were obtained from ImaGenes. Plasmid DNA from clones was isolated for DNA sequencing (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. Cloned cDNAs in the purified plasmid DNA were sequenced by Iontek Laboratory (Istanbul, Turkey). Nucleotide and translated amino acid sequences were compared with known sequences using BLAST algorithms (National Center for Biotechnology Information, Bethesda, MD). Following the confirmation of the selected clone, His-tagged protein was recombinantly expressed in Escherichia coli, purified by affinity chromatography and the purity of the protein was documented by SDS-PAGE analysis (Fig. 1), as reported previously (Preuss et al., 2009).

2.3. Immunoblotting analyses

The purified protein was denatured (100 °C, 5 min). 1 μg purified protein was loaded in each lane, electrophoresed (10% acrylamide gel) and transferred to 0.45-μm polyvinylinedene fluoride membranes (100 V, 80 min). Membranes were blocked (5% milk in TBST; 90 min) and incubated with individual human sera (diluted 1:200) or commercially available rabbit anti-human antibody (1:200 dilution) (Santa Cruz Biotechnology, Santa Cruz, CA) followed by HRP-conjugated goat anti-human IgG or goat anti-rabbit IgG (Jackson ImmunoResearch Laboratory) at 1:1000 dilutions. Immunoreactivity was visualized on chemiluminescent film using ECL Western blotting substrate (Pierce, Thermo Scientific, USA) according to the manufacturer’s instructions (Fig. 1).

2.4. ELISA

Detection of antibodies to the purified recombinant human protein was performed with ELISA. The purified protein (50 μl at 10 μg/ml) was added to the wells of a 96-well high-binding-capacity plate and incubated overnight at 4 °C. Wells coated with the E. coli lysate or only with bovine serum albumin were used as controls. The plates were washed with TBST and blocked for 2 h with 5% skim milk in TBS. A 60 μl aliquot of each serum sample (diluted 1:100) in TBST was added to protein coated wells and incubated for 2 h at room temperature. The plates were washed six times with TBST followed by the addition of 60 μl of alkaline phosphatase-conjugated goat anti-human IgG (Southern Biotech, Birmingham, AL, USA) diluted 1:200 in TBST and then incubated at room temperature for 1 h. After washing, 60 μl of 2-(2-benzothiazoyl)-6-hydroxybenzothiazole phosphate was added for 45 min at room temperature followed by addition of the stopping solution (3 N NaOH). Fluorescent signals were measured at 450/50 excitation and 580/50 emission with a microplate reader. For each sample, the value obtained from the protein-coated well was subtracted from the non-coated well. The obtained results were expressed as signal ratios (sample signal/mean signal of healthy controls). Positivity was defined as 2 standard deviations above the mean of healthy controls.

2.5. Immunohistochemistry and colocalization studies on rat brain sections

Whole rat brain was treated first with 4% paraformaldehyde overnight at 4 °C, immersed in 40% sucrose overnight at 4 °C and subsequently snap frozen in liquid nitrogen. Seven μm-thick frozen sections were serially incubated with 0.3% H2O2 for 20 min, 10% goat serum for 1 h at room temperature and serum samples (1:200) overnight at 4 °C. They were then incubated in biotinylated goat anti-human IgG

Fig. 1. Coomassie blue-stained 10% SDS-PAGE analysis of purification of mitochondrial carrier homolog 1 (Mtch1) yielding a band at around 40 kDa, as predicted (leftmost column), and representative immunoblots for Western blot analysis of recombinant Mtch1 protein (remaining 5 columns). While both commercially available rabbit anti-human Mtch1 antibody (Mtch1-Ab) and neuro-Behçet’s disease (NB) patients’ sera that were found to be positive for Mtch1 Ab by ELISA (NB p) yielded ~40 kDa bands at the Mtch1 protein loaded gels, NB sera that were seronegative for Mtch1 Ab by ELISA (NB n) did not show any bands.
intensity of apoptosis was estimated in NBD patients and healthy controls by measuring serum levels of circulating nucleosomes with a quantitative sandwich-enzyme-immunoassay, using mouse monoclonal antibodies directed against DNA and histones, respectively. This method allowed specific detection and quantitation of histone-associated DNA fragments in mono- and oligonucleosomes (a marker for apoptotic cells) that are released into serum. Serum levels of nucleosomes were measured as per manufacturer’s protocol (Roche Applied Science, Indianapolis, IN, US).

2.7. Statistics

Demographic and clinical features of NBD patients were compared using Fisher’s exact test, Student’s t-test or Mann–Whitney U test, as appropriate. Signal ratios obtained in ELISA experiments were compared among groups by ANOVA and Tukey’s post-hoc test. Serum nucleosome levels were compared with Student’s t-test. Correlation statistics were performed with parametric Pearson’s or non-parametric Spearman’s correlation tests, as required. A p value smaller than 0.05 was considered as statistically significant.

3. Results

3.1. Identification and verification of Mtch1 antibody

To identify target antigens of NBD-associated neuronal autoantibodies, a protein macroarray derived from a human fetal brain cDNA expression library was used to screen sera from NBD patients. A single clone with the highest signal intensity and number of duplicates (n = 3) was selected for further investigation. DNA sequencing and BLAST analysis of the clone yielded a single oligonucleotide that corresponded to 92% of the sequence of Mtch1 (GenBank accession number, NM_014341). A Mtch1 his-tagged fusion protein was recombinantly produced in E. coli and purified by affinity chromatography. SDS-PAGE analysis showed a single band at around 40 kDa, consistent with the predicted molecular weight, confirming the purity of the obtained protein (Fig. 1).

ELISA studies performed with the recombinant protein revealed high-titer autoantibodies in 18 of 32 (56.3%) NBD, 50 of 112 (44.6%) BD, 3 of 47 (6.4%) multiple sclerosis, 1 of 21 (4.8%) neuromyelitis optica patients and none of the healthy controls (Fig. 2). Overall, 68 of 144 (47.2%) BD patients with or without neurological involvement and 4 of 168 (2.4%) non-BD controls displayed Mtch1 antibody corresponding to a sensitivity of 47.2% at 97.6% specificity. NBD and BD patients had significantly higher signal ratio values as compared to control groups (p<0.0001 by ANOVA and p<0.05–0.001 by Tukey’s post-hoc test, Fig. 2). None of the sera reacted with the lysate of the E. coli strain (data not shown), supporting the specificity of the autoantibody measurements. There were no significant differences between average signal ratios of BD patients with (2.3 ± 1.9) or without (2.6 ± 1.7) immunosuppressive treatment (p = 0.148 by Student’s t-test).

![Image](https://via.placeholder.com/150)

Fig. 2. ELISA detection of IgG antibodies directed against mitochondrial carrier homolog 1 (Mtch1) in sera of neuro-Behçet’s disease (NBD) patients, Behçet’s disease patients with no neurological involvement (BD), multiple sclerosis patients (MS), neuromyelitis optica patients (NMO) and healthy controls. The dashed lines represent 2 standard deviations (2SD) above the mean of the healthy control samples (cut-off values for positivity). Horizontal lines indicate the mean value of each group. *, p < 0.05; **, p < 0.01; ***, p < 0.001 by Tukey’s post-hoc test.
Mtch1 antibody seropositivity rates were also comparable among both groups (23/58 patients with immunosuppression vs 27/54 patients without immunosuppression, \( p = 0.431 \) by Fisher's exact test).

The antibody binding to Mtch1 was confirmed by Western blotting using purified Mtch1 protein. Both the commercially available antibody to Mtch1 and the seropositive NBD sera reacted with a band at the predicted 40 kDa, whereas seronegative sera did not show any immunoreactivity (Fig. 1). In immunohistochemistry studies, serum IgGs of Mtch1 antibody positive NBD patients showed strong cytoplasmic reactivity with neurons located throughout the whole brain section, including cerebellar Purkinje cells and cortical neurons (Fig. 3A,B), whereas those of Mtch1 antibody negative NBD patients did not show any appreciable immunoreactivity. Mtch1 is located at the mitochondrial membrane and is thus a cytoplasmic protein (Xu et al., 2002; Lamarca et al., 2007). Therefore, the cytoplasmic staining pattern obtained by NBD sera was considered to be due to immunoreactivity with neuronal Mtch1 protein. Immunofluorescence studies performed with sera of NBD patients and a commercially available Mtch1 antibody revealed a significant co-localization of reactivities with seropositive (Fig. 3C–E) but not seronegative (Fig. 3F–H) serum samples, further confirming the presence of Mtch1 antibodies.

**3.2. Comparison of clinical features among Mtch1 antibody positive and negative NBD patients**

NBD patients with and without Mtch1 antibodies did not significantly differ in terms of gender, age, clinical course, disease duration, neurological disability and pathergy test positivity. Although a higher antibody positivity rate was observed in samples obtained during a neurological attack, this difference did not attain statistical significance (\( p = 0.165 \) by Fisher’s exact test). By contrast, Mtch1 antibody positive patients had significantly higher number of NBD attacks prior to blood sampling than Mtch1 antibody negative patients (\( p = 0.024 \) by Student’s \( t \)-test). Also, Mtch1 antibody positive patients showed trends towards exhibiting higher Expanded Disability Status Scale (EDSS) scores (\( p = 0.094 \) by Mann–Whitney \( U \)) and parenchymal rather than vascular NBD findings (\( p = 0.142 \) by Fisher’s exact test) (Table 1).

**3.3. Differential apoptotic cell death in Mtch1 antibody positive and negative patients**

Mtch1 has been implicated to take part in apoptotic cell death mechanisms (Xu et al., 2002; Lamarca et al., 2007). To investigate whether
Comparison of clinical and demographic features of neuro-Behçet’s disease (NBD) patients with and without mitochondrial carrier homolog 1 antibodies (Mtch1-Ab).

<table>
<thead>
<tr>
<th>Mtch1-Ab negative (n = 14)</th>
<th>Mtch1-Ab positive (n = 18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (women/men)</td>
<td>6/8</td>
<td>7/11</td>
</tr>
<tr>
<td>Age (mean ± SE)</td>
<td>34.8 ± 2.2</td>
<td>37.5 ± 2.6</td>
</tr>
<tr>
<td>Patients with samples obtained during an attack</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Patients with parenchymal/vascular NBD</td>
<td>7/7</td>
<td>14/4</td>
</tr>
<tr>
<td>Duration of NBD during serum sampling (years; mean ± SE)</td>
<td>10.6 ± 1.9</td>
<td>9.5 ± 1.7</td>
</tr>
<tr>
<td>Number of attacks before serum sampling (mean ± SE)</td>
<td>1.3 ± 0.1</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Patients with positive pathergy test</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>EDSS scores (mean ± SE)</td>
<td>1.5 ± 0.4</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Patients with relapsing remitting/progressive clinical course</td>
<td>12/2</td>
<td>17/1</td>
</tr>
</tbody>
</table>

SE; standard error, CSF; cerebrospinal fluid, EDSS; expanded disability status scale.
<sup>a</sup> Fisher’s exact test.
<sup>b</sup> Student’s t-test.
<sup>c</sup> Mann–Whitney U test.

The presence of Mtch1 antibodies alters apoptotic cell death rates, the intensity of apoptosis was estimated in sera of 32 NBD patients and an equal number of healthy controls (randomly selected from healthy control samples used in ELISA studies) using a cell death detection kit based on quantitation of circulating nucleosomes. NBD patients had significantly higher serum nucleosome levels than healthy controls (p = 0.0001 by Student’s t-test, Fig. 4A). Notably, Mtch1 antibody positive NBD patients had significantly lower nucleosome levels than Mtch1 antibody negative NBD patients (p = 0.034 by Student’s t-test, Fig. 4B). In line with these results, Mtch1 antibody signal ratio values of NBD patients were negatively correlated with their circulating nucleosome levels (R = −0.474, p = 0.047 by Pearson’s test).

4. Discussion

A number of autoantibodies have been described in serum and/or CSF samples of NBD patients. Most of these are directed against stress-related proteins, such as HSP-60, HSP-65, HSP-70, c-B-crystallin and stress-induced-phosphoprotein 1. Antibodies to PINK1, α-enolase, cyclic citrullinated peptide and S. cerevisiae antigens have also been identified. However, all of these antibodies are found only in a small fraction (5–35%) of NBD patients and they can also be frequently detected in patients with other neuroinflammatory diseases lowering their values as a diagnostic biomarker (Taşci et al., 1998; Tanaka et al., 1999; Celet et al., 2000; Fresko et al., 2005; Koca et al., 2007; Birtas-Atesoglu et al., 2008; Lee et al., 2009; Vural et al., 2009; Vural et al., 2011). Annexin-V antibodies are highly prevalent in NBD and BD patient cohorts (Gheita et al., 2012), but can be detected in a plethora of rheumatological disorders (Iaccarino et al., 2011) and the prevalence in other neuroinflammatory disorders is currently unknown. The novel Mtch1 antibody described in this study does not only add a new member to the list of NBD-associated antibodies but also appears to be a potential diagnostic biomarker with its high frequency in NBD patients and low prevalence in other neuroinflammatory diseases that are in the differential diagnosis list of NBD such as multiple sclerosis.

Presently, the only reliable diagnostic test for BD and NBD is the pathergy test, which also constitutes a part of the BD diagnostic criteria. However, problems with standardizing the induction method, needle size and type as well as the method of assessment of the response have limited the usefulness of this test in the clinical setting. Also, the prevalence of a positive pathergy test in BD varies among countries and test centers. Sensitivity of the pathergy test ranges between 30% and 45% at specificities of 87% to 100% (Dilşen et al., 1993; Chang and Cheon, 2002; Ozdemir et al., 2008; Davatchi et al., 2011). The sensitivity and specificity values of Mtch1 antibodies for NBD and BD patients in our study were easily comparable with those of pathergy test. As a matter of fact, the frequency of Mtch1 antibody seropositivity in our NBD cohort (56.3%) was higher than that of pathergy test positivity (53.1%). Therefore, ELISA-based Mtch1 antibody measurement might potentially be utilized as a reliable, easy-to-use, noninvasive and standard diagnostic method.

NBD almost always develops several years after the onset of BD (Akman-Demir et al., 1999) and thus NBD patients are generally under immunosuppressive treatment. Although we managed to avoid the effects of steroid treatment on Mtch1 seropositivity, since all of our NBD patients were under long-term follow-up as BD patients, we could not compare Mtch1 antibody levels in naïve and immunosuppressed NBD patients. Nevertheless, this comparison was made among BD patients. Although non-immunosuppressed BD patients showed trends towards exhibiting slightly higher Mtch1 antibody levels than immunosuppressed BD patients, this difference did not reach statistical significance, suggesting that measurement of Mtch1 antibody is not significantly affected from immunosuppression and lower Mtch1 antibody seropositivity rates in the BD group is not related with the differences in treatment status. However, for a better assessment of the specificity of Mtch1 antibody, patients with non-inflammatory CNS disorders as well as other vasculitic–rheumatological disorders need to be studied.

Based on the molecular mimicry between stress induced proteins and certain proteins expressed by microorganisms, it has recently been proposed that HSP antibodies develop as a result of the immune reaction against invading pathogens and coincidentally crossreact with human tissue thus causing BD symptoms (Ghasemi et al., 2012). However, our extensive search in National Center for Biotechnology Information GeneBank using BLAST and CLC Main Workbench software has failed to find any considerable identity between Mtch1 and proteins of a wide range of microorganisms (data not shown). Moreover, Mtch1 antibody’s association with NBD disease severity and apoptotic cell death rates

Fig. 4. Intensity of apoptosis in neuro-Behçet’s disease (NBD) patients vs healthy controls (A) and NBD patients with vs without mitochondrial carrier homolog 1 antibodies (Mtch1-Ab) (B) estimated by serum levels (OD) of circulating nucleosomes measured using a cell-death detection ELISA kit. *, p < 0.05; ***, p < 0.001 by Student’s t-test.
suggests that Mtch1 antibody is not a bystander side effect of auto-
inflammation and might have certain pathogenic functions in NBD path-
ogenesis. It is well known that, in BD, an increased occurrence of
apoptotic cell death is observed in parenchymal lesions of CNS as well
as other involved tissues (Hirohata, 2008). Notably, both Mtch1 and
recently identified BD autoantigen annexin-V are associated with apo-
ptosis and levels of antibodies to both antigens are correlated with dis-
ease severity (Xu et al., 2002; Lamarca et al., 2007; Iaccarino et al.,
2011; Gheit et al., 2012). Mtch1 is a proapoptotic protein, Mtch1 anti-
bodies tend to occur in patients with a more severe disease course and
patients with Mtch1 antibodies exhibit reduced intensity of apoptotic
cell death, altogether suggesting that Mtch1 antibodies might plausibly
be developing as a protective mechanism to reduce and neutralize the
tissue damage affdicted by BD associated autoimmunization. Antibodies
to progranulin, a protein associated with frontotemporal dementia,
have recently been discovered in vasculitis patients (Thurner et al.,
2012). Notably, Mtch1 is closely associated with presenilin, the dysfunc-
tion of which might cause Alzheimer’s disease (Xu et al., 2002; Lamarca
et al., 2007). Whether these recent findings point to a possible link
between neurodegeneration and neuroinflammation requires to be scru-
tinized in future studies.

In conclusion, Mtch1 antibody seropositivity appears to have a con-
siderable sensitivity and specificity for NBD and BD. The association be-
tween Mtch1 antibody levels and clinical and apoptotic parameters of
NBD suggests that Mtch1 antibody might have a pathogenic action.
Therefore, further characterization of the functional role of Mtch1 anti-
body is warranted.

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