Journal of the Neurological Sciences 362 (2016) 100–105

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Optic neuritis with positive HLA-B27: Characteristic phenotype in the Chinese population☆

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ARTICLE INFO

Article history:
Received 3 November 2015
Received in revised form 11 January 2016
Accepted 15 January 2016
Available online 18 January 2016

Keywords:
Optic neuritis
HLA-B27
Multiple sclerosis
Neuromyelitis optica
Ankylosing spondylitis
Autoimmune diseases
Aquaporin 4

ABSTRACT

Purpose: This study retrospectively reviewed the clinical features of optic neuritis (ON) with positive HLA-B27.
Method: Clinical data were reviewed for HLA-B27-positive ON in the Chinese People's Liberation Army General Hospital from January 2009 through June 2015. The prevalence of HLA-B27 and spondyloarthropathies was analyzed. Clinical features of HLA-B27-positive ON based on serum aquaporin 4-antibody (AQP4-Ab) were compared.
Results: A total of 22 ON patients (14 female/8 male, 38 involved eyes) with positive HLA-B27 were collected from 410 ON patients. Recurrent episodes were observed in 14/22 patients, and seven patients presented as bilateral simultaneous ON. A total of 68.4% (22/38) of involved eyes exhibited severe visual impairment (<0.1) at onset. A total of 8/22 patients were seropositive for AQP4-Ab, and clinical features did not differ based on AQP4-Ab status. Bilateral sacroiliitis was revealed in over 50% (7/13) of patients screened using pelvic computed tomography. Three patients were diagnosed with ankylosing spondylitis (AS), and one patient experienced co-occurrence of active AS and bilateral ON.
Conclusions: HLA-B27-positive ON may presented recurrent episodes and severe visual impairment at onset. The co-occurrence of ON and AS, and the frequent presence of bilateral sacroiliitis may indicate an underlying alternation of autoimmune background in this condition.

1. Introduction

Optic neuritis (ON) is an acute inflammatory optic neuropathy that is generally associated with primary autoimmune demyelination or astrocytic pathology, and it is often the first manifestation of multiple sclerosis (MS) or neuromyelitis optica (NMO) [1]. Accompanying autoimmune disorders (e.g., lupus and Sjögren's syndrome) or autoantibodies are frequent in ON [2].

HLA-B27 is located on all nucleated cells, platelets and reticulocytes, and it may provide an alternate immune background that is closely linked to the intraocular inflammatory disease acute anterior uveitis (AAU) and the extraocular disorder spondyloarthropathies (SpA), especially ankylosing spondylitis (AS) [3]. The pathogenesis in SpA and AAU shares some comparable hypotheses, including molecular mimicry of bacterial peptides for the induction of specific regulatory T cells and cross-reactive auto-antibodies. Therefore, "B27 disease" is widely accepted as an autoimmune disorder [4].

Pillay (1986) reported delayed visual-evoked potentials (VEPs) in 60% of B27-positive AS patients [5]. The association between AS and central nervous system demyelination was hypothesized subsequently. ON may be the initial presentation for AS [6], and it may co-occur with active AS [7,8]. An underlying link between HLA-B27 and ON was hypothesized based on these studies.

The present study investigated the clinical features of B27-positive ON and assessed extraocular SpA in a neuro-ophthalmologic center in China.

2. Methods

2.1. Patients

ON patients who underwent HLA-B27 tests in the ON database of Chinese People's Liberation Army General Hospital (PLAGH) from Jan. 2009 through June 2015 were screened to identify positive cases.

☆ **Ethical Standard**: This study was approved by the PLAGH Ethics Committee and was conducted following the Declaration of Helsinki in its currently applicable version.

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http://dx.doi.org/10.1016/j.jns.2016.01.027
0022-510X/

The diagnosis of ON followed the Optic Neuritis Treatment Trial (ONTT) Group [9]. MS and NMO were confirmed using the 2010 revisions to the McDonald criteria [10] and Wingerchuk's 2006 diagnostic criteria [11], respectively. Modified New York criteria were used for the diagnosis of AS [12].

2.2. Ophthalmological and associated examinations

Ophthalmological examinations included slit lamp inspection, the swinging-light test for RAPD, and direct or indirect ophthalmoscopy with dilated pupils for retinal examination. Best-corrected visual acuity (BCVA) was tested using a Snellen chart. A Humphrey SITA 30-2 protocol was used in perimetry when BCVA was better than 0.1. Peripapillary retinal nerve fiber layer (RNFL) circle scans and macular thickness measurements were performed using a spectral-domain optic coherence tomography (OCT) device.

2.3. Blood and cerebrospinal fluid (CSF) tests

Blood was drawn from all ON patients for erythrocyte sedimentation rate (ESR) and c-reaction protein (CRP) analyses, total anti-nuclear antibodies (ANAs) titer, autoantibodies against double-stranded DNA, Sjögren's syndrome A (SSA)/B (SSB), Scl-70, Jo-1, proliferating-cell nuclear antigen, cardiolipin, neutrophil cytoplasmic antigen, rheumatoid factor and HLA-B27 in the rheumatological research center in PLAGH. Assays of AQP4-Ab using cell-based assays were performed as previously described [13].

CSF was collected via lumbar puncture in 21/22 patients for cell counts and total protein, glucose and chloride levels. Another examination for oligoclonal band (OCB) was performed for each sample.

2.4. Imaging

Ocular and/or brain magnetic resonance imaging (MRI) was performed in all patients. Spinal MRI was performed for patients with seropositive AQP4-Ab and positive neurological signs. T2-weighted imaging (T2WI) and post-contrast T1WI was used for image collection. A total of 13/22 patients underwent pelvic computed tomography (CT) to evaluate bilateral sacroiliac joints.

2.5. Treatment

The management of acute ON followed the suggestion of ONTT using an intravenous high-dose methylprednisolone (IVMP) for 3–5 days, followed by a gradual taper [9]. Oral azathioprine or mycophenolate mofetil were chosen for long-time management after IVMP in patients with seropositive AQP4-Ab. Three AS patients received no specific treatment other than non-steroid anti-inflammatory drugs.

2.6. Statistical analysis

Statistical analyses were performed using the Statistical Program for Social Sciences statistical software (version 21.0; IBM SPSS, Inc., Chicago, IL). Categorical data were analyzed using the Chi-squared test or Fisher's exact test, and p values < 0.05 were considered significant.

3. Results

3.1. Demographic manifestations

The data of 22 ON patients (38 involved eyes) with positive HLA-B27 was collected from 410 ON patients who underwent HLA-B27 screening. The prevalence of HLA-B27 was 5.4% (22/410) in ON patients. The ethnicity of all patients was Han Chinese. The mean age at ON onset was 36.2 (ranged 10–60) years with a female/male ratio of 1.75:1. The average disease duration was 36.1 (ranged 4–127) months. Two patients met the diagnostic criteria for NMO or MS, and three patients were diagnosed as AS. Table 1 shows the demographic characteristics of ON patients.

3.2. Clinical profiles

All patients had no history of uveitis. The ophthalmologic examination finds no evidence for newly onset or remote uveitis. The involvement of bilateral eyes was observed in 72.7% (16/22) of patients. Fourteen patients (63.6%) presented as recurrent episodes, and 7 patients exhibited the simultaneous involvement of bilateral eyes. Fig. 1 presents relapses throughout the disease duration for each patient.

A total of 68.4% (22/38) of involved eyes exhibited severe visual impairment (<0.1) at onset, which decreased to 31.6% (12/38) during the follow-up period of an average 19.8 (ranged 3–62) months. Table 2 presents VA at nadir and the last follow-up for each patient.

3.3. Supplementary laboratory findings

The inflammatory indicators ESR (88 mm/h, normal range 0–20 mm/h) and CRP (10.7 mg/L, normal range 0–0.8 mg/dL) were markedly elevated in one patient (number 7 in Table 2). A total of 10/22 patients exhibited positive results in the accompanying autoantibody tests (Table 2). Comparisons of clinical profiles based on the status of serum AQP4-Ab revealed no significant differences (Table 3). CSF tests revealed elevated protein levels with normal white cell counts in 3 cases, and negative OCB in all samples.

3.4. Evaluations of VF and OCT

VF defect types included peripheral defect (10 eyes), mainly quadrant defect (6 eyes), diffuse defect (2 eyes) and central scotoma (1 eye) in 20 testable eyes of 12 patients, which did not differ between AQP4-Ab-positive and AQP4-Ab-negative groups (Table 3). Two patients with acute ON with AS presented with an asymmetrical thickening of peripapillary RNFL, as revealed on OCT (Fig. 2).

3.5. Imaging and accompanying autoimmune diseases

T2 hyperintensity (with or without enhancement) was revealed in all of the involved optic nerves using orbital MRI. SS was diagnosed in one patient (number 9 in Table 2) on salivary gland biopsy. One patient (number 2 in Table 2) was diagnosed with Hashimoto's thyroid disease.

Bilateral sacroiliitis was confirmed in 7/13 patients on pelvic CT scan, and 3 patients were diagnosed with AS (Table 4). A rheumatologist (J. Z.) diagnosed a 31-year-old male patient (number 7 in Table 2) with a co-occurrence of ON and active AS evaluated. Definite AS was excluded in the remaining 9 patients who did not undergo pelvic CT because of the absence of clinical symptoms.

3.6. Response to treatment

Responses to IVMP varied in each ON attack. Seven of 8 AQP4-Ab-positive ON patients exhibited a decrease in annual relapse rate with

Table 1
Demographic characters of HLA-B27-positive optic neuritis.

Numbers of patients (n)	22
Involved eyes (n)	38
Ethnicity	*All Han Chinese*
Sex ratio (F/M)	1.75:1
Age at onset (mean ± SD, y)	36.2 ± 15.40
Disease duration (mean ± SD, m)	36.1 ± 31.25
Definite NMO (n)	1
Definite MS (n)	1

Abbreviations: NMO: neuromyelitis optica; MS: multiple sclerosis.