CASE REPORT

Crescentic glomerulonephritis in a patient with neuromyelitis optica (Devic´s syndrom)

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Abstract

Neuromyelitis optica (NMO) or Devic´s syndrome is an inflammatory, demyelinating disease of the central nervous system leading to optical neuritis and myelitis. Etiology of NMO is unknown, although autoimmune disorders involving IgG autoantibodies specific for aquaporin 4 are suspected. These autoantibodies are associated with 73% sensitivity 93% specificity for NMO helping to distinguish NMO from other demyelinating disorders. Some cases of NMO are reported in association with systemic lupus erythematosus and Sjögren`s syndrome. Here we report a patient presenting with NMO and concomitantly occurring rapid progressive crescentic intra- and extracapillary crescentic glomerulonephritis.

Keywords

Crescentic glomerulonephritis, Devic´s syndrom, NMOSD, Renal failure

1 Introduction

Neuromyelitis optica (NMO) or Devic´s syndrome is an inflammatory, demyelinating disease of the central nervous system (CNS) leading to optic neuritis and myelitis [1]. Consensus guidelines for diagnosis are: optic neuritis, acute myelitis and at least two minor criteria which consist of 1) spinal cord lesions extending three or more vertebral segments in magnetic resonance imaging (MRI), 2) cerebral MRI not consistent with diagnostic criteria for multiple sclerosis (MS) and 3) detection of NMO-specific IgG antibodies in patient's serum [2]. Pathogenesis of NMO is still not fully understood. Recent studies suggest humoral mechanisms to be causally involved in the development of NMO [3-5]. B-cell derived autoimmunity has been observed in most patients presenting with NMO [6]. Lennon and coworkers [7] described IgG type autoantibodies that specifically bind to aquaporin 4 (AQP4) exerting a sensitivity of 73% and a specificity of 93% for the diagnosis of NMO.

These autoantibodies are used to differentiate NMO from other demyelinating disorders. Interestingly these autoantibodies also bind to AQP4 located in microvessels, pia, subpia and Virchow-Robin sheats in the CNS [8]. However, AQP4 expression is not restricted to CNS solely. It is also expressed in the renal collecting duct, connecting tubules, gastric parietal epithelial cells, skeletal muscle, airway and exocrine gland epithelium [1, 9]. However, some patients do not have

detectable autoantibodies. Often NMO is coincident with autoimmune diseases like systemic lupus erythematosus, Sjögren`s syndrome, Hashimoto thyroiditis, gluten sensitivity or myasthenia gravis [10-15].

Here we report about a patient who presented with neuromyelitis optica and coincidently with rapidly progressive crescentic intra- and extracapillary immune complex glomerulonephritis.

2 Case report

A 23 year old Caucasian male presented to our neurological department with nuchal pain, emesis and progressive bilateral visual impairment within a time frame of ten days prior to admission. Besides schizophrenia treated with haloperidol and clozapine no pre-existing illnesses of the body could be elucidated. In addition the patient had a chronic abuse of amphetamine and cannabis and heroin.

Ophthalmological examination revealed a bilateral optic neuritis with severely impaired acuity of 0.1. MRI and computer tomography (CT)-scans of the brain did not show any abnormal findings. Especially no signs congruent with McDonald's criteria for the diagnosis of MS were found [16].

Apart from hypoesthesia of the right half of the body including pain, temperature and tactile sensation neurological as well as physical examinations of the heart, lung and abdomen were inconspicuous at the time of admission. Blood pressure was 150/80 mmHg, heart rate 64 beats per minute and respiratory frequency was 15 breaths per minute.

Biochemical and hematological analyses were within normal ranges except a slightly elevated serum creatinine of 1.5 mg/dl (0.5-1.4 mg/dl), elevated creatine phosphokinase (CK) of 394 U/l (< 171 U/l) and minimally decreased hematocrit of 39% (40%-52%).

Examination of cerebrospinal fluid (CSF) showed an increased protein level of 1064.6 mg/l (< 500 mg/l) without pleocytosis. There was no evidence for intrathecal synthesis of IgG or disruption of the blood-brain barrier. Oligoclonal bands were not detected. Test results for glucose, lactate and albumin were within normal range.

Seven days after admission the patient rapidly developed disturbance of gait with progressive paraparesis, positive Babinski´s reflex and disturbance of micturition with a residual urine volume of 150 ml. Renal function deteriorated and serum creatinine peaked at 3.2 mg/dl, serum urea at 114 mg/dl, respectively. Our patient developed pronounced peripheral edema without pulmonary overload or cardiac tamponade.

Urine sediment showed erythrocyturia lacking leukocytes or evidence of urinary tract infection. Neither acellular nor cellular casts nor acanthocytes could be detected. Proteinuria was considerably with a protein-to-creatinine ratio of 9.

Since autoimmune or rheumatic disorders like polymyositis, vasculitis or systemic lupus erythematodes were feasible we performed multiple immunological screening tests including anti-nuclear antibodies (ab), anti-ds-DNA, -RNP, -SM, -SSA, -SSB, -ScL70, -Jo1, -cytoplasmatic ab, liver kidney microsomes ab, anti-mitochondrial ab, anti-GBM ab, smooth muscle ab, actin ab, parietal cell and reticulum ab, cryoglobulins, complement factors C3 and C4.

All of the above mentioned parameters were negative or within normal ranges. C3 (NV 0.5-1.8 g/l) and C4 (NV 0.1-0.4 g/l) slightly but insignificanty declined from 1.1 to 0.8 g/l and 0.28 to 0.18 g/l respectively. Blood tests for bacterial, parasitical or viral infections including hepatitis B and C as well as HIV and HTLV were also negative.

Due to progressive neurological impairment a repeated MRI scan showed increased T2-signal intensity from C3 - C7 without contrast enhancement, whereas MRI of the brain was still normal (see Figure 1).

Thus, despite a normal NMO IgG antibody level (antibody-ratio 9.06 [NV < 10]) the diagnosis of NMO was made since McDonald's criteria of MS were not fulfilled.

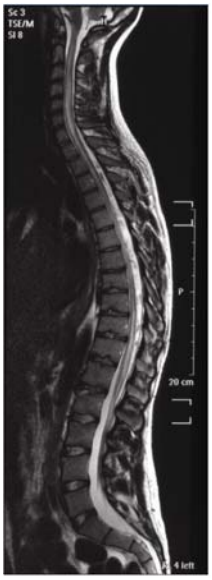

Figure 1. Sagittal T2-weighted TSE MRI of the entire spine shows extensive intramedullary signal abnormalities with a major focus in the cervical spine.

Consequently, a methylprednisolone pulse therapy applying 1 gram per day intravenously for 5 consecutive days was started according to general recommendations [17, 18]. After the steroid pulse therapy paraparesis ameliorated, visual capacity and neurological status improved. Above-mentioned hyperintensities in the spinal MRI scans were declining.

As renal impairment persisted the patient was transferred to the nephrological department. Abdominal ultrasound displayed normal sized kidneys with echointense parenchyma and fading distinction between cortex and marrow. Urine analysis showed a non-selective proteinuria without casts or leucocytes.

However, since the pathogenesis of renal impairment was unclear, we performed a kidney biopsy to establish diagnosis. Histological examination showed a severe intra- and extracapillary immune complex glomerulonephritis. The mesangium exhibited accented granular deposits of IgG, IgA, IgM, C3 and occasionally fibrinogen. Sixteen out of twenty-two glomeruli were affected and depicted pronounced mesangial matrix expansion, hypercellularity and cellular crescents together with disruption of Bowman's capsule. Furthermore, the biopsy revealed advanced tubular atrophy and interstitial fibrosis with foci of resorptive infiltrates (see Figure 2a-b).

Consequently, immunosuppressive therapy was intensified including prednisolon and cyclophosphamid. Prednisolon was started with 100 mg per day for five days, and then reduced to 1 mg per kg body weight per day (75 mg/d). Cyclophosphamid was administered at a dose of 2 mg per kg body weight per day (150 mg/d). Hypertension was treated with candesartan 8 mg twice a day. Additionally the patient received simvastatin 40 mg once a day.

Within three weeks of immunosuppression kidney function improved and serum creatinine decreased to 2.3 mg/dl; proteinuria also improved and declined to a protein-to-creatinine ratio of 3.3.

Simultaneously, neurological impairments ameliorated further. A repeated spinal cord MRI demonstrated merely spinal edema at C6/7. One week later the patient was discharged. Visual acuity improved to 0.6 on the left and 0.8 on the right eye, locomotion on short distance was possible without assistance and the indwelling catheter could be removed.

The patient was looked after monthly in our outpatient clinic for a time frame of 12 months and did well. Then he stopped therapy and was lost for follow-up. Two and a half years after the primary onset he presented again with end stage renal disease so that renal replacement therapy had to be initiated. By contrast, the degree of neurological pathology was still stable.

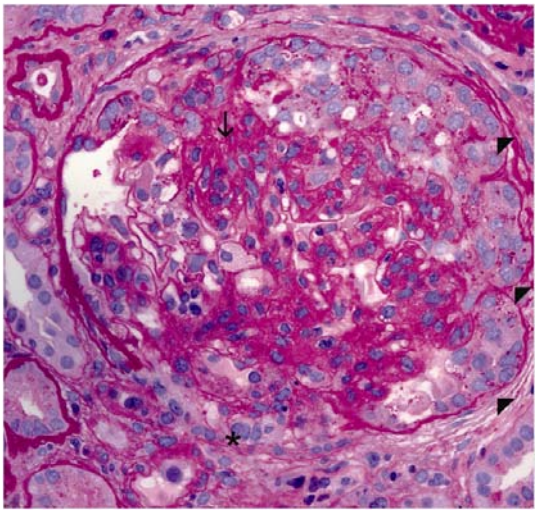

Figure 2a. PAS staining 40× times magnified.
Intra- and extracapillary proliferative glomerulonephritis with pronounced mesangial matrix expansion and hyper-cellularity (→) as well as cellular crescents (►) with partial disruption of Bowman's capsule (*).

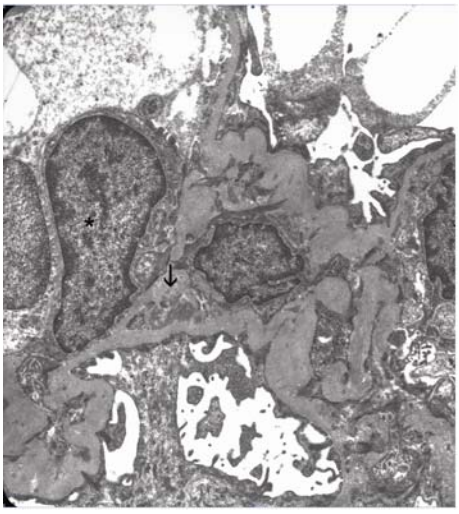

Figure 2b. Electron micrograph at 4000× times magnification.
Depicts typical electron-dense immune-complex deposit (→) in the glomerular mesangium, adjacent to the nucleus of a mesangial cell (centre). Eendothelial cell nuclei (*).

3 Discussion

Wingerchuck et al define NMO as a demyelinating syndrome of the central nervous system. After revision of consensus criteria for the diagnosis of NMO [2] the term "NMO spectrum disorders" (NMOSD) was introduced to mirror the various and diverse clinical and radiological manifestations of NMO including those cases of NMO with co-existing systemic autoimmune diseases [19].

Etiology of NMO is not fully understood. Some authors suggest a key role of B-cell derived humoral autoaggression due to those cases of NMO that present with associated autoimmune diseases like lupus erythematosus or Sjögren`s syndrome [10-15]. Furthermore, NMO-IgG autoantibodies in NMO patient's sera as well as the response to immunosuppressive therapy suggest an autoimmune origin of the disease [7, 10, 20-22].

Autoantibodies directed to aquaporin 4, that is a water-pump channel protein associated with cerebral microvessels and endothelial foot processes have also been discussed to play a pathogenic role [23]. However, our patient may suffer from a somewhat different peculiarity of NMO since we could not prove NMO-specific antibodies. In line with this is the observation that NMO-IgG autoantibodies are not detectable in 20%-30% of NMO patients [19]. Assay sensitivities may differ and thus may explain some negative results [24]. Time and frequency of blood sampling seems to be another important confounder. Commonly patients are tested during onset of clinical symptoms or after initiation of therapy and thus may falsely appear seronegative for NMO autoantibodies [25]. Seronegative patients usually show no gender preference, but a higher proportion of monophasic courses of NMO and often a Caucasian descent [19]. In contrast, seropositive patients exhibit higher frequencies of extensive spinal cord and brain lesions [3].

Upon examination spinal lesions of eighty-two patients with clinically confirmed NMO showed extensive macrophage infiltration and perivascular diffuse deposition of immunoglobulins, mainly IgM and complement C9 neo antigen as well as C1q, C3-C8. These deposits may initiate nonspecific inflammatory reactions comprising complement activation and cytokine release finally leading to both vascular and parenchymal tissue damage [26].

In 2008 Pittock et al. [27] retrospectively evaluated the correlation of NMO with other autoimmune disorders in a blinded serological survey and demonstrated a general predisposition to multiple autoimmune diseases in NMO patients. Recently, Wingerchuck and Weinshenker postulated that NMO and autoimmune diseases are coexisting conditions in patients susceptible to autoimmunity and may occur in up to 30% [7, 28]. Conversely, the hypothesis that NMO is just a complication of autoimmune diseases appears unlikely since autoimmune disease is expected consistently to be diagnosed first [27].

Neo-antigens derived from apoptosis may lead to the induction of autoantibody formation that could be linked to glomerular disease. We only can hypothesize that either antibodies or immune complexes both charged highly cationic might have occurred during the disease process thus having the potential do deposit at the glomerular basement membrane [29, 30].

Although we cannot prove such a pathogenetic process, it may reflect a putative mechanism of disease. Another explanation for our observations may be that the patient suffered from a mere co-existence of two independent diseases not connected to one another.

Nonetheless, we ought to consider the unexpected onset of a glomerular disease with renal insufficiency as a hint to scrutinize the patient for the coincidentally existence or impending appearance of NMO.

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