Optimization of Laboratory Diagnostics of Neuromyelitis Optica Spectrum Disorders: Indications and Algorithms

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Abstract

Neuromyelitis optica spectrum disorders are a group of autoimmune demyelinating diseases of the central nervous system characterized by severe exacerbations with development of residual neurological deficit. Anti-aquaporin-4 antibody is a key factor in diagnosing, differentiating, and prescribing pathogenetic therapy. The paper discusses indications for tests and methods of detecting anti-aquaporin-4 antibodies.

***Keywords**: neuromyelitis optica spectrum disorders; laboratory diagnostics; anti-aquaporin-4 antibodies.*

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Оптимизация лабораторной диагностики заболеваний спектра оптиконевромиелита: показания и алгоритмы

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Аннотация
Заболевания спектра оптиконевромиелита – группа аутоиммунных демиелинизирующих заболеваний центральной нервной системы, которые характеризуются тяжёлыми обострениями с формированием остаточного неврологического дефицита. Определение антител к аквапорину-4 является ключевым фактором диагностики, дифференциальной диагностики и назначения патогенетической терапии. В статье обсуждаются вопросы показаний к назначению исследования и методик определения антител к аквапорину-4.

Ключевые слова: *заболевания спектра оптиконевромиелита; лабораторная диагностика; антитела к аквапорину-4*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are a group of severe autoimmune demyelinating diseases of the central nervous system (CNS) that share a common pathogenic mechanism of complement-dependent astrocytopathy induced by the production of antibodies to aquaporin-4 (AQP4-IgG) [1]. This term expands the long-used diagnosis of neuromyelitis optica (Devic's disease) because NMOSD can be identified in the early stages of the disease, allowing timely initiation of pathogenetic therapy to prevent exacerbations, which are a significant contributor to the persistent disability of patients [2]. Differential diagnosis of NMOSD with other immune-mediated CNS disorders, especially multiple sclerosis (MS), is necessary because many disease-modifying treatments can cause severe exacerbations of NMOSD [3–8]. According to diagnostic criteria proposed in 2015, the diagnosis of NMOSD should be established not only using the clinical and radiological picture, but also considering such a key aspect as AQP4-IgG based on cell antigen presentation [9].

In Russia, three agents are approved for the prevention of exacerbations of NMOSD, including satralizumab, eculizumab, and ravulizumab. They proved to be effective in seropositive forms of NMOSD in which AQP4-IgG was detected [10–12]. AQP4-IgG detection is therefore a critical test required for both the diagnosis of NMOSD and the selection of pathogenetic treatment. However, the AQP4-IgG assay has some challenging aspects, such as the limited

availability of laboratory kits in Russia [13], the influence of treatment on test results [14], as well as the use of other methods that are not based on antigen cell presentation, such as enzyme-linked immunosorbent assay (ELISA) [15]. Therefore, it is necessary to clarify the indications for primary and repeat testing for AQP4-IgG and to develop an algorithm for the laboratory diagnosis of NMOSD. The authors analyzed and discussed the scientific literature on the laboratory diagnosis of NMOSD, particularly the determination of AQP4-IgG, and proposed recommendations for initial and repeat testing of patients for AQP4-IgG.

Methods for Determination of Autoantibodies

The source of the antigen is a critical component of all autoantibody detection methods. Anti-neuronal antibody assays often use neuronal antigens from laboratory animals. Tissue sections are used as the so-called tissue substrates for antibody binding which is assessed by indirect immunofluorescence or immunohistochemistry for autoantibodies. In neuroimmunology, such tissue substrates traditionally include cryosections of the cerebellum, hippocampus, optic nerve, and smooth muscle neural plexi from laboratory rodents or primates (macaques). Since many antigens are present in the tissue, the obvious advantage of this approach is the possibility of multiple detection of different autoantibodies by determining different staining types of the tissue [16]. However, accurate identification of detected antibodies requires verification assays using a predetermined autoantigen. In addition, this method may have low sensitivity due to the low tissue expression of most proteins [17]. The Mayo Clinic laboratories first discovered AQP4-IgG using this tissue assay. This was done using indirect immunofluorescence on cryosections of rodent cerebellum, stomach, and kidney, confirmed by immunoprecipitation [18, 19].

ELISA or immunoblotting methods using protein molecules, most of which are genetically engineered, are commonly used to characterize autoantibody serum spectra. The solid phase is polystyrene plastic materials of ELISA plates or different types of nitrocellulose membranes [20]. Such methods are suitable for identifying a wide range of antineuronal antibodies directed against structural proteins localized in the nucleus and cytoplasm of neurons (e.g. Hu, Ri, Yo-1, etc.). In addition, the ELISA is traditionally used to detect antibodies against gangliosides or other myelin components (anti-MAG).

The antigenic epitopes of most neural tissue proteins expressed on the cell membrane have a complex lipid bilayer-bound conformation which is irreversibly destroyed when the proteins are released from the cell and attempt to adhere to the solid phase. Complex methods were used to address this issue. For this reason, radiolabelled α-bungarotoxin was used to detect antibodies to the acetylcholine receptor, allowing the autoantibody detection in solution. However, the limited range of high-affinity receptor antagonists made it difficult to study autoantibodies to transmembrane channels and nervous tissue receptors. Other methods using labelled recombinant proteins include fluorescence immunoprecipitation or radioimmunoprecipitation, which ensure antibody-antigen interaction in solution, but their sensitivity for detecting antineuronal antibodies is low [21].

Assays with cell expression of antigens and genetically modified cells are based on transfection of eukaryotic cell lines (most commonly the embryonic kidney line HEK293) with plasmids containing a nucleotide sequence that encodes the target protein. When expressed, significant amounts of protein either accumulate in the cell cytoplasm or become exposed on cell membranes [22].

Transfection can be classified as transient and stable. Transient transfection is a relatively rapid and simple technique, but stable transfection provides a higher level of sensitivity. Flow cytometry, confocal microscopy, and indirect immunofluorescence are used to detect autoantibody and protein binding, with non-transfected cells used as a negative control [23]. In addition, some commercially available substrates contain a pre-optimized mixture of transfected and non-transfected cells of the same line to facilitate visual assessment of reaction results.

Flow cytometry and confocal microscopy are suitable for live cell assays and are considered by some authors to be the most sensitive methods for the detection of antineuronal antibodies to membrane antigens [24]. Their clinical use is limited by the need for cell line maintenance in the laboratory and difficult standardization.

Recently, indirect immunofluorescence using fixed adhesion cell lines has become widespread. The method of fixation depends on the cellular localization of the protein. For membrane localization of the target protein, special fixatives such as glutaraldehyde, paraformaldehyde, or formalin are used, and for cytoplasmic localization, additional fixation is used to increase the permeability of cell membranes. Since the HEK293 cell line is an embryonic kidney line that normally synthesizes aquaporins, the expression and processing of the AQP4 protein result in the appearance of AQP4 on the cell membrane [25].

The ability to use ready fixed cell preparations ensures the standardization of the cell substrate of autoantibody detection methods between laboratories, making them accessible to the majority of clinical laboratories. The result of antibody detection on fixed cells is expressed as a final titer, which is inversely proportional to the last dilution of serum that gives a positive signal (Figure 1). Using flow cytometry and confocal microscopy, the intensity of

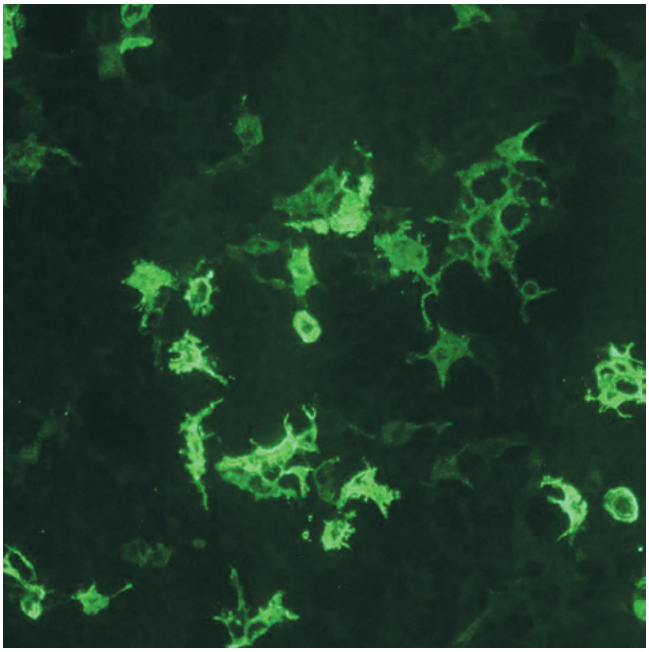

Fig. 1. Positive test result for anti-AQP4 antibodies. Indirect immunofluorescence with antigen cell presentation, 1 : 1000 titer, fluorescence intensity +++.

the fluorescent signal can be quantified. Due to their high sensitivity, cell-based antigen expression assays have become the recognized gold standard for the detection of many types of antineuronal antibodies, including anti-AQP4-IgG and anti-myelin oligodendrocyte glycoprotein (MOG) IgG [9].

Aquaporin-4 as an Autoantibody Target

AQP4 is a member of a family of 13 transmembrane water channels consisting of 6 alpha-helical domains spanning the cell membrane within which the water channel is located. Two types of AQP4, the longer (AQP4-M1) and the shorter (AQP4-M23), are expressed in the body. The shorter AQP4-M23 can form orthogonal arrays of particles with higher affinity for AQP4-IgG in the membrane, making the M23 isoform a preferred target of autoantibodies [21]. In the CNS, AQP4 protein is found as orthogonal clusters predominantly on astrocytes around small brain vessels, which are the primary target of the immune response in NMOSD.

In multicenter studies, the average sensitivity for the detection of AQP4-IgG using cellular antigen expression methods is 76.7% [21]. Some respected researchers reported high sensitivity of in-house flow cytometry or confocal microscopy methods using live transfected cells compared to commercially available kits [26]. This is especially helpful with borderline confounding results where nonspecific membrane staining can make a specific reaction difficult to detect. For example, some laboratories, including the Mayo Clinic laboratory, use flow cytometry with live transfected cells, which has an 80% sensitivity and a 100% specificity [27]. However, in-house assays are challenging due to the significant variability in transfection quality. Fixation of transfected cells to membranes prevents nonspecific reactions caused by other common autoantibodies, such as antibodies to mitochondria or antinuclear factor. AQP4-IgG is a highly specific indicator of NMOSD, as the false positive rate for AQP4-IgG in patients with classic MS using the autoantigen expression in cells assay is only 0.1% [28]. By contrast, autoantibody detection by recombinant-antigen enzyme immunoassay has a low sensitivity (63–64%) and a relatively high incidence of false positive reactions (0.5–1.3%) [21].

In comparison to many other antineuronal antibodies, synthesis of AQP4-IgG is predominantly systemic. Studies of large collections of paired blood serum and cerebrospinal fluid samples show that in all cases, autoantibodies are more frequently detected in the blood and the titers are higher [29]. Asymptomatic carriage of AQP4-IgG has been described [30], while some seronegative patients may seroconvert at diagnosis [31], and some patients have seroreversion during successful immunosuppressive therapy [14].

Clinical Phenotypes Requiring Anti-Aquaporin-4 Antibody Testing

The classic phenotypes of NMOSD have 6 clinical manifestations: the most common ones include optic neuritis (ON), acute myelitis, *area postrema* syndrome (the chemoregulatory center at the floor of the fourth ventricle) characterized by uncontrollable nausea, vomiting, and hiccups. Less common manifestations include acute brainstem lesion, acute diencephalic syndrome (with symptomatic narcolepsy and/or endocrine disorders), and hemisphere injury. The latter two manifestations are always associated with symptomatic lesions on magnetic resonance imaging (MRI) [9].

According to the scientific literature, serum testing for the presence of AQP4-IgG is recommended for all patients with suspected NMOSD [9, 32]. The term "suspected NMOSD" is interpreted differently by different authors, and there are no precise guidelines for prescribing the test that would be absolutely clear to clinicians. The first proposed indications included longitudinal extensive transverse myelitis (LETM); acute idiopathic transverse myelitis (TM) with signs that are not typical for MS; severe ON with poor recovery, simultaneous bilateral ON, extensive optic nerve injury or chiasmal involvement on MRI; intractable (difficult to control) nausea, vomiting, or hiccups in the absence of gastrointestinal disorders; MRI lesions of the dorsal medulla oblongata; clinically significant diencephalic disorders (hypersomnia, narcolepsy, endocrine disor-

ders characteristic of hypothalamic pituitary dysfunction); cryptogenic leukoencephalopathy; and suspected MS with unexplained severe exacerbations on treatment with disease-modifying agents for MS [33, 34].

Other guidelines recommend AQP4-IgG testing in patients with LETM without focal MRI brain changes or with brain lesions not characteristic of MS; with frequent recurrent ON; with diencephalic syndrome with unspecified focal changes, and with encephalopathy of unknown nature [35–37]. In 2020, V.S. Krasnov et al. recommended expanding the proposed indications to include newly developed partial TM or ON, regardless of severity of neurological dysfunction and recovery level [38]. This recommendation is supported by the data from routine clinical practice. In 8 (28.6%) of 27 NMOSD patients with AQP4-IgG, the first exacerbation manifested as partial TM or unilateral ON with subsequent regression of symptoms, so the test was not performed, resulting in a longer delay in diagnosis. The relevance of this recommendation is confirmed by the fact that 5 (62.5%) of these 8 patients were subsequently misdiagnosed with MS and treated with MS-modifying agents, which can worsen the course of NMOSD [2–5].

Back in 2007, NMOSD experts recommended that optic nerve or spinal cord injury in a patient with systemic lupus erythematosus or Sjögren's syndrome should be considered a manifestation of concomitant NMOSD rather than a neurologic complication of rheumatic disease due to vasculitis [39]. This recommendation was re-confirmed in 2015 [9]. Later, Latin American experts concluded that patients with a known systemic autoimmune disease with clinically apparent ON, acute TM, or *area postrema* syndrome should be tested for blood AQP4-IgG [40]. In 2023, Russian neurologists proposed some new indications for this test including a neuroimaging sign such as extensive ($\geqslant$ 3 vertebral segments) spinal cord atrophy on MRI, as well as cases not inconsistent with the diagnosis of MS but without oligoclonal antibodies detected in cerebrospinal fluid [41].

In 2023, the Neuromyelitis Optica Study Group (NEMOS) published a consensus paper recommending testing for AQP4-IgG in all patients with clinical or radiologic findings (both current and historical) that suggest a diagnosis of NMOSD. This includes all patients with one of the main clinical syndromes of NMOSD, including ON, acute myelitis, *area postrema* syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome with typical diencephalic MRI lesions, cerebral syndrome with typical hemispheric MRI lesions. Experts also recommend testing in all cases where the patient is diagnosed with NMOSD according to the 2015 diagnostic criteria without AQP4-IgG or an unknown status for antibodies to AQP4. In all other cases, the decision to test or not to test should be made on a case-by-case basis. It has also been suggested that AQP4-IgG screening in MS patients who do not meet the above criteria, especially in regions where NMOSD represents only a small percentage of idiopathic inflammatory demyelinating diseases, may increase false positive results and is not recommended [42]. The above guidelines require clarification of the type of brainstem manifestations for which the test should be performed. It is recommended to limit them to the most common oculomotor disorders, facial paresis, facial numbness, and ataxia, which are the most common in brainstem syndrome [42, 43].

Similar recommendations have been proposed for children, as the main clinical manifestations of NMOSD and the diagnostic criteria are similar to those for adults [44]. 50–75% of pediatric patients have ON at onset, with 50% having bilateral ON [45, 46]; 30–50% of patients with NMOSD have TM, although LETM is less common in children with NMOSD compared to that in adults and may be present in acute disseminated encephalomyelitis. In contrast, acute diencephalic syndrome, especially endocrinopathies, and symptomatic cerebral syndrome are more common in the pediatric population with NMOSD than in adults: up to 60% and up to 16–32%, respectively [47, 48]. Neuroimaging in pediatric patients shows large confluent lesions with vasogenic edema (a phenotype similar to acute disseminated encephalomyelitis). Lesions often involve the corticospinal tract and periventricular region, and nonspecific hemispheric white matter lesions are also visualized [49]. The frequency of AQP4-IgG seropositivity in children with NMOSD is significantly lower than in adults. A study of pediatric NMOSD in the United States showed that only 65% of children were seropositive for AQP4-IgG, and in some cases, antibodies were not detected until 3 years after disease onset [50]. Moreover, MOG-IgG is much more prevalent in the pediatric NMOSD population than in adults [51].

Special attention should be paid to situations where routine testing is not recommended. AQP4-IgG testing was considered inappropriate for patients with ON if it did not meet strictly defined criteria as mentioned above, or in the presence of clinical, MRI, and laboratory signs typical of MS, so as not to increase the number of false positive results [33, 34]. However, this position is contradicted by data demonstrating the possibility of a mild ON at the onset of NMOSD [38], as well as information that the detection of oligoclonal IgG in CSF does not exclude the diagnosis of NMOSD, which occurs in 20–43% of patients with NMOSD, especially at the time of exacerbation, but may be transient and not detected in subsequent samples [9, 40]. Since AQP4-IgG is a highly specific test and the reported incidence of initial MS misdiagnosis in NMOSD patients is 33.0–42.5% [27, 32], clinicians often use the test beyond the above indications in an attempt to avoid misdiagnosis.

Possible Causes of False Positive and False Negative Results

Causes of false laboratory results for AQP4-IgG testing can occur at both the pre-laboratory and laboratory stages. False negative results are most often caused by pre-laboratory factors. These include noncompliance with patient preparation rules, including general conditions (test to be done in the morning and in fasting state, no fatty food or alcohol the day before, limited physical activity, no hypothermia/hyperthermia, no smoking 1 hour before testing) and special conditions such as sampling after or during pathogenetic therapy (corticosteroids, plasmapheresis, immunosuppressive agents, monoclonal antibodies, that prevent NMOSD exacerbations) [52].

Observations of antibody status in patients undergoing repeat AQP4 IgG testing are of particular interest. In China, 400 NMOSD patients with AQP4-IgG who were receiving immunosuppressive therapy were evaluated. At a median follow-up of 3.7 years, 32% of patients had seroreverted to seronegative status and no AQP4-IgG was detected. These patients had a lower incidence of exacerbations, and a direct relationship was found between time to seronegative status and exacerbations [14].

The Mayo Clinic (USA) followed patients who were tested at least twice for AQP4-IgG. Out of 986 NMOSD patients with AQP4-IgG, 53 patients had a negative result at baseline, i.e. they experienced a seroconversion to seropositive status (more than 9,000 patients were tested with a baseline negative result), and 6 patients were tested during treatment (corticosteroids, plasmapheresis, azathioprine, natalizumab). Of 933 NMOSD patients initially positive for AQP4-IgG, 11% demonstrated seroreversion at a mean of 1.2 years. This was observed mainly in young patients (up to 20 years of age) and in patients with initially low titer of AQP4-IgG. Seroreversion has been reported with anti-B-cell therapy, azathioprine, mycophenolate mofetil, plasmapheresis, and autologous stem cell transplantation. Half of the patients with seroreversion experienced subsequent seroconversion [53].

A seronegative window has also been proposed when AQP4-IgG is either completely bound to the antigen, making detection impossible, or present at a concentration insufficient for detection but sufficient to cause clinical manifestations, as it was demonstrated for *area postrema* syndrome [54].

Causes of false positive results are much less common and may be related to the presence of tuberculosis. Aquaporins of *Mycobacterium tuberculosis* and human AQP4 may have homologous epitopes, which can lead to cross-reactivity, whereas AQP4-IgG titers are usually higher in tuberculosis than in NMOSD. Natalizumab enhances the membrane surface presentation of AQP4, so patients treated with this drug may also have false positive AQP4-IgG assay results [55].

False AQP4-IgG assay results may be due to errors in the pre-analytical and analytical laboratory phases. The most common pre-analytical errors include non-compliance with sample collection, transportation, and storage (repeated freezing/thawing), significant hemolysis or milky white serum. False negative errors in the laboratory include the hook effect which is an immunological phenomenon of decreased affinity of antibodies to form immune complexes when the concentration of antibodies is very high. This phenomenon is important for clinical practice because it interferes with the analysis and can lead to false negative results [56]. There are some other reasons for false negative results, such as a defect in the microslide or non-compliance with a test procedure (overdrying of the microslide during the staining, burning out of the microslide after long exposure to microscope light) [57].

Due to the high complexity of this assay, many skills are needed, both in indirect immunofluorescence and in this specific assay. Therefore, insufficient operator experience may lead to false positive results (interpretation of non-specific fluorescence as specific for AQP4-IgG) [58]. However, the antibodies can be present at the borderline level (⩽1:10), which can be referred to as non-specific fluorescence (Figures 2–5).

The prognosis of NMOSD can be based on factors such as the age of onset, the number of exacerbations during the first 2 years, the severity of the first exacerbation, the association with other autoimmune diseases, and the serologic status of AQP-IgG [59]. Many studies have shown a lower rate of recovery of visual impairment after exacerbation in patients with AQP4-IgG compared to seronegative patients [60]. A prospective study of 29 patients with isolated LETM found that only 55% of AQP4-IgG seropositive patients had no exacerbations at 1 year, while none of seronegative patients had exacerbations [61]. Given the significant risk of new exacerbation in the first year after disease onset, it is recommended to perform 2-3 repeat tests within 6-12 months after the initial negative result [62]. Since repeat assay in repeatedly seronegative patients increases the risk of false positive results, AQP4-IgG "seroconversion" of previously seronegative patients should ideally be confirmed by further assay [34].

Recommendations for AQP4-IgG Testing

The following are the basic principles of how and for which clinical and radiologic phenotypes the AQP4-IgG assay should be performed for the first time, as well as at what time point the assay should be repeated.

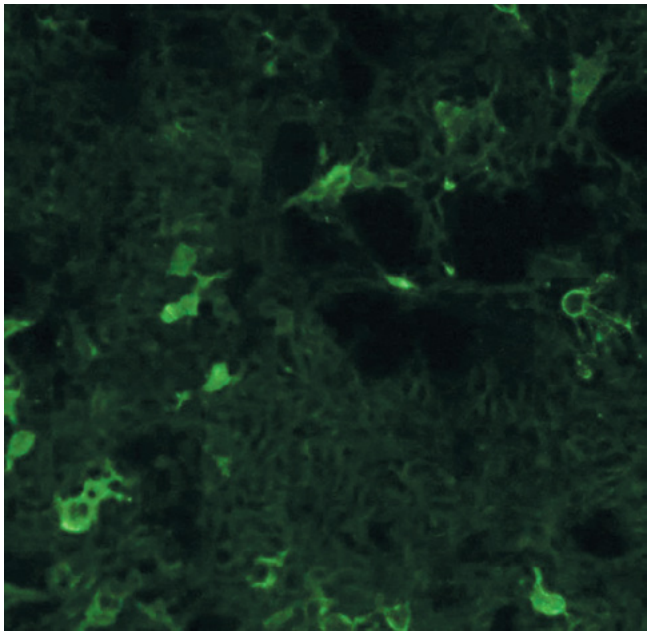

Fig. 2. Positive test result for anti-AQP4 antibodies.
Indirect immunofluorescence with antigen cell presentation, 1 : 10 titer, fluorescence intensity ++.

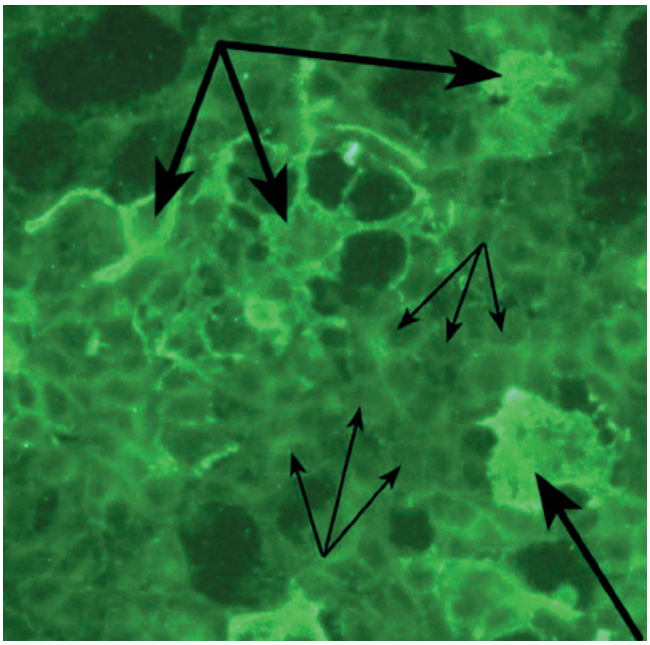

Fig. 3. Positive test result for anti-AQP4 antibodies.
Indirect immunofluorescence with antigen cell presentation, 1 : 320 titer, fluorescence intensity ++ (thick arrow) with areas of nonspecific fluorescence (thin **arrows).**

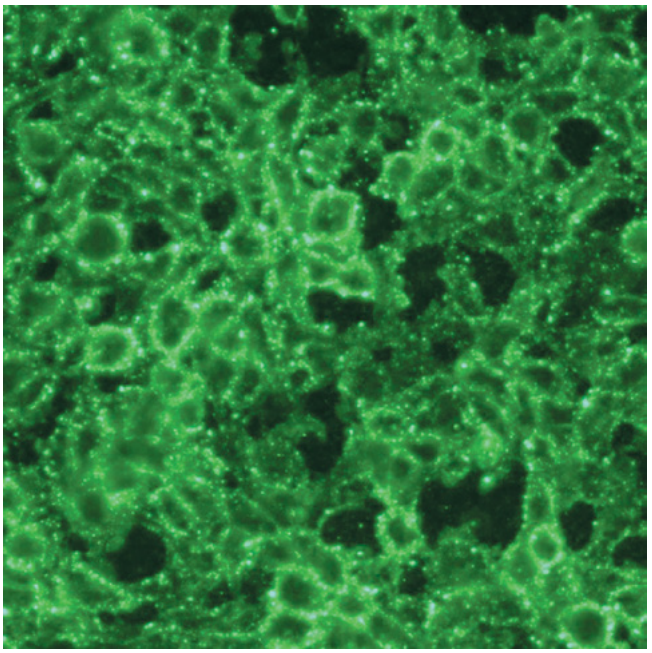

Fig. 4. Negative test result for anti-AQP4 antibodies to be confirmed by repeat test.
Indirect immunofluorescence with antigen cell presentation, nonspecific fluorescence (+/–).

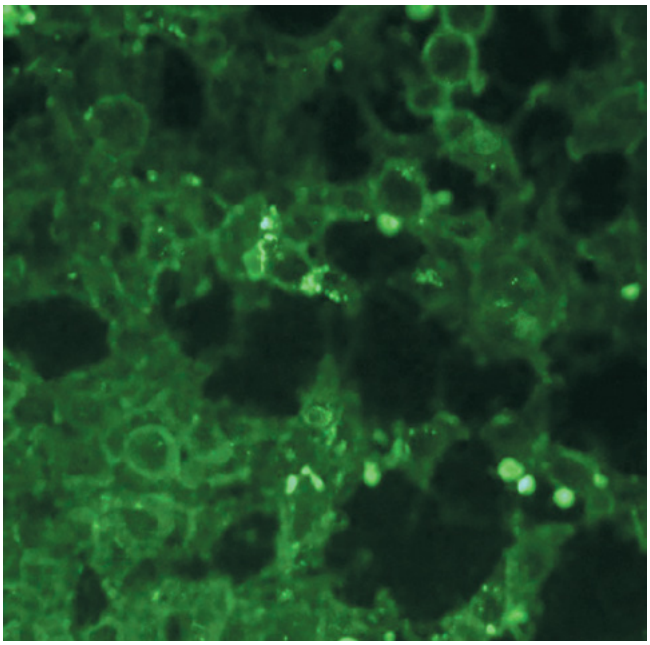

Fig. 5. Negative test result for anti-AQP4 antibodies to be confirmed by repeat test.
Indirect immunofluorescence with antigen cell presentation, nonspecific fluorescence (+/–).

1. Serum testing for anti-AQP4 antibodies should be performed in all patients with suspected NMOSD by indirect immunofluorescence with antigen cell presentation (enzyme immunoassay is not recommended).
2. NMOSD is suspected when a patient has:
   1) 1 of 6 main acute/subacute clinical syndromes (both current and historical):
      a) ON (severe ON with poor recovery; bilateral ON; extensive optic nerve injury or chiasmal involvement on MRI; frequent recurrent ON; ON as the first disease manifestation regardless of its severity; ON in a patient with systemic autoimmune disease),
      b) acute myelitis (LETM, acute idiopathic TM with signs that are not typical for MS; TM as the first disease manifestation regardless of its severity; TM in a patient with a systemic autoimmune disease; extensive (⩾ 3 vertebral segments) spinal cord atrophy on MRI indicating history of acute/subacute myelopathy),
      c) *area postrema* syndrome (in the absence of gastrointestinal disorders and other causes such as vestibular disorders, infectious diseases, intoxication, drug therapy, endocrine disorders, stroke, neoplasms), including a known systemic autoimmune disease,
      d) isolated acute brainstem syndrome (oculomotor dysfunction, facial paresis, facial numbness, ataxia, symptomatic brainstem injury involving periepidermal areas),
      e) symptomatic narcolepsy or acute diencephalic syndrome (hypersomnolence, syndrome of inappropriate antidiuretic hormone release) with typical diencephalic MRI lesions not clearly explained by other causes,
      f) acute cerebral syndrome (hemiparesis or tetraparesis, visual field loss, varying degrees of consciousness disorders, epileptic seizures) with typical unspecified hemispheric MRI lesions (cryptogenic leukoencephalopathy with characteristic MRI brain changes),
   2) suspected MS with unexplained severe relapses on treatment with MS-modifying agents,
   3) suspected MS with clinical manifestations of at least one of the main NMOSD syndromes, atypical clinical manifestations, and the absence of oligoclonal IgG in the CSF (the presence of oligoclonal IgG in the CSF does not exclude NMOSD). However, a reliable diagnosis of MS based on clinical and radiologic features (McDonald criteria 2017) in the absence of the above signs does not suggest NMOSD.
3. When submitting biomaterial for anti-AQP4 testing, the stage of disease (exacerbation or remission), the sampling time (before, during, or after corticosteroid and plasma exchange/immunoadsorption therapy), and the name of the drug if treated with drugs to prevent exacerbations should be provided.
4. To reduce the risk of a false negative result, serum samples for serum anti-AQP4 testing should be collected prior to initiation of corticosteroid pulse therapy, plasmapheresis/plasma exchange therapy, or treatment with drugs to prevent exacerbations.
5. AQP4-IgG test results should include information on the antibody titer, the technique used, and the presence or absence of non-specific fluorescence for AQP4-IgG.
6. If an initial negative result (< 1 : 10) is obtained and NMOSD is still suspected, repeat the AQP4-IgG test after 3-6 months and/or in case of repeated exacerbations.
7. If an initial positive result is 1 : 10 or there are clinical, neuroimaging, or laboratory changes that require clarification of NMOSD diagnosis (red flags), or there is nonspecific fluorescence for AQP4-IgG, repeat the assay after 1 month.
8. Two or three repeat assays may be performed within 6–12 months of an initial negative result, as well as after 12 months, depending on the clinical situation. The upper limit of 12 months is due to the significant risk of re-exacerbation of NMOSD in the first year.
9. Patients diagnosed with NMOSD with AQP4-IgG who are receiving therapy to prevent exacerbations may experience seroreversion (reversion to a seronegative status), which does not require repeat testing and is not a reason to discontinue or change therapy.

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