Neuromyelitis Optica: Diagnosis, Pathogenesis, and Treatment

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Although the co-occurrence of myelitis and optic neuritis that characterizes neuromyelitis optica (NMO) was recognized over a century ago, distinguishing NMO from multiple sclerosis relied solely on clinical criteria until recently. The identification of a biomarker that has high specificity for NMO is clinically useful for distinguishing NMO from multiple sclerosis and identifying patients at high risk for recurrent myelitis and optic neuritis. That fact that the biomarker is an autoantibody that recognizes aquaporin 4 (AQP4), a water channel expressed on astrocyte podocytes, has substantially contributed to the hypothesis that NMO is a humorally mediated autoimmune disease. This review discusses the discovery of the NMO-IgG biomarker, the identification of AQP4 as its target, the clinical applications of these advances, the pathologic implications for the anti-AQP4 antibody, and advances in NMO treatment.

Introduction

Neuromyelitis optica (NMO) is an inflammatory, demyelinating, chronic central nervous system (CNS) disease characterized by recurrent, severe attacks of myelitis and optic neuritis. The disease was first described in the late 18th century and was the source of much debate as to whether it constituted a distinct disease or was simply a form of multiple sclerosis (MS). Recently, a biomarker for NMO, NMO-IgG, was identified. This autoantibody binds to aquaporin 4 (AQP4), a water channel ubiquitously expressed throughout the CNS and in the stomach and kidneys. Because this autoantibody is reasonably sensitive and highly specific for NMO, it is useful diagnostically in distinguishing NMO from typical MS. Whether the autoantibody participates in the pathogenesis of NMO is not proven; however, several recent studies implicate AQP4 as a target for autoimmune-mediated injury (Table 1). Apparently successful treatments with plasmapheresis for acute flares and with B-cell depletion for maintenance of remission support the concept that NMO may be, at least in part, a humorally mediated disease.

Discovery of NMO-IgG

NMO-IgG was discovered at the Mayo Clinic by Lennon et al. [1] in 2004 through recognition of an unusual immunohistochemical staining pattern using a rat brain slice preparation to identify novel paraneoplastic autoantibodies. A distinct pattern characterized by staining of the subpial and Virchow-Robin spaces of unclear etiology was recognized. When serum from a patient suffering from NMO was found to have the same staining pattern, the researchers obtained serum samples from additional NMO patients from North America and a cohort of Japanese patients with opticospinal MS. Thirty-five of 45 patients who had NMO based on clinical criteria were found to have the same unique staining pattern (73% sensitivity). An additional cohort of 14 patients whose serum had undergone paraneoplastic antibody assessment and were known to have this staining pattern was retrospectively identified and their medical records were obtained. Remarkably, every case reviewed was found to have a history consistent with NMO or recurrent transverse myelitis. Subsequent investigation in a cohort of 22 patients who presented with optic neuritis and myelitis but who were considered to have MS and not NMO identified only two patients as testing positive for the antibody (91% specificity). Thus, without knowing the target for the antibody, a biomarker for NMO was found.

Clues to the antigen recognized by the antibody came from the immunohistochemical staining pattern. The antibody stained the abluminal face of cerebral microvessels and the pericapillary regions of astrocytes. Furthermore, it colocalized with laminin. The antibody also recognized distal urine-collecting tubules in the renal medulla and parietal cells in the gastric mucosa. This distribution pattern led to the hypothesis that the antigen recognized by the NMO-IgG was AQP4, a water channel [2]. AQP4 is the predominant water channel in the CNS [3]. It is expressed

Table 1. Observations supporting a role for humoral autoimmunity in NMO pathogenesis

100% of NMO plaques have antibody and complement depositions compared with 60% of MS plaques [18]
Seropositivity for anti-AQP4 antibodies differentiates NMO from MS [1,2]
Anti-AQP4 titers correlate with the length of hyperintensity on spinal cord MRI at the nadir of myelitis [16]
Anti-AQP4 titers decline during remissions induced by immune suppression [16]
Class 1 IgG anti-AQP4 antibodies cause AQP4 to be endocytosed from cell surface membranes of transfected HEK cells in vitro [23]
Class 1 IgG anti-AQP4 antibodies cause deposition of Cneo9 complement on cell surface membranes of transfected HEK cells in vitro [23]
AQP4 reactivity is loss from acute NMO plaques [17•,19,21,22]
The pattern of loss of AQP4 reactivity corresponds to the pattern of deposition of antibody and complement in NMO plaques [19]
Acute NMO attacks respond to treatment with plasmapheresis [34,35]
Rituximab and mitoxantrone deplete B cells and may induce remissions in NMO [43•,47•]

AQP4—aquaporin 4; HEK—human embryonic kidney; MS—multiple sclerosis; NMO—neuromyelitis optica.

at high concentrations in astrocyte foot processes facing microvessels, interneuronal synaptic junctions, and ventricular ependyma. It is coexpressed with the potassium channel Kir4.1, is associated with the dystrophin protein complex, and regulates water flux between brain and blood and brain and spinal fluid [4]. AQP4 appears to be crucial for elimination of interstitial water, and deletion of AQP4 appears to exacerbate vasogenic edema.

In a series of experiments, Lennon et al. [5••] tested their hypothesis that NMO-IgG bound to AQP4. First, NMO-IgG serum was found to not bind to CNS tissue from transgenic mice carrying deletions of the AQP4 genes. Second, NMO-IgG serum recognized human embryonic kidney (HEK) cells transfected with the AQP4 gene. Third, NMO-IgG serum immunoprecipitates green fluorescent protein labeled AQP4 but not other members of the dystroglycan complex proteins. These elegant experiments conclusively proved that the antigen recognized by the NMO-IgG antibody was AQP4. Both the immunohistochemical and the AQP4-transfected HEK cell assays for detecting anti-AQP4 antibody from patient sera were subsequently validated by several groups [6–8].

Diagnosis of NMO and Utility of the Anti-AQP4 Antibody

Multiple sets of diagnostic criteria for NMO previously were proposed in the literature [9]. Using data abstracted by retrospective review of 71 cases, Wingerchuk et al. [10] proposed diagnostic criteria that incorporated clinical characteristics as well as neuroimaging and cerebrospinal fluid studies. Although these criteria were apparently quite useful, they were derived empirically rather than systematically and were not validated prospectively. Because the anti-AQP4 antibody could reliably differentiate NMO from typical MS, a revision was made of the proposed diagnostic criteria for NMO. After testing several models, Wingerchuk et al. [11•] simplified and restructured the criteria as follows: 1) optic neuritis; 2) acute myelitis; and 3) at least two of three supportive criteria: i) contiguous spinal cord lesion extending three or more spinal cord segments, ii) brain MRI not meeting criteria for MS, and iii) NMO-IgG seropositivity. These criteria allowed inclusion of NMO patients who tested seropositive for NMO-IgG but who had brain MRI lesions, extraoptic nerve and spinal cord clinical manifestations, or milder attacks. These revised criteria were 99% sensitive and 90% specific for differentiating NMO from MS with optic nerve and spinal cord presentations.

Although the cerebrospinal fluid profile and attack-related motor weakness criteria were also validated, these NMO features had less diagnostic power and were dropped from the final model. Notably, visual characteristics other than a history of optic neuritis were not included in the revised criteria. The utility of the revised criteria was validated in an independent, prospectively gathered dataset that found the revised criteria to have greater specificity (83.3% vs 25%) but lower sensitivity (87.5% vs 93.7%) than the 1999 criteria [12]. Furthermore, positive (87.5% vs 62.5%) and negative (83.3% vs 75%) predictive values both were improved with the revised criteria.

Anti-AQP4 antibody is clinically useful not only for differentiating between NMO and MS with optic nerve and spinal cord presentations, but also for its predictive value following acute attacks of myelitis. In a retrospective study, 55% of patients presenting with myelitis who were seropositive for the anti-AQP4 antibody experienced a second demyelinating event of either recurrent myelitis or optic neuritis during the next year compared with 0% of seronegative patients [13•]. Interestingly, in a study of recurrent optic neuritis, seropositivity for the anti-AQP4 antibody was associated with only a 50% risk of myelitis over an 8.9-year median follow-up interval [14]. Three separate cases of seropositive recurrent optic neuritis during 9 to 12

years of follow-up never developed transverse myelitis [15]. These cases of anti-AQP4 antibody–seropositive recurrent optic neuritis suggest that either another factor in addition to anti-AQP4 antibody is necessary for patients to develop myelitis or that an inhibitor of myelitis may be present in some patients, restricting involvement to the optic nerves.

A study by Takahashi et al. [16] found a correlation between anti-AQP4 antibody titer and optic neuritis and myelitis severity. Higher titers of anti-AQP4 antibodies were present in patients with complete blindness or cavitary lesions on brain MRI. Spinal cord MRI at the nadir of myelitis also correlated with higher anti-AQP4 antibody titers. Anti-AQP4 antibody titers declined following treatment with high-dose methylprednisolone and remained low during periods of remission induced by immune suppression. These observations provide supportive evidence that the anti-AQP4 antibody is also a biomarker for disease activity in NMO.

The Anti-AQP4 Antibody and Pathogenesis

The identification of the anti-AQP4 antibody was a major breakthrough in understanding the immunobiology of CNS demyelination. For the first time, an autoantibody that was not also found in healthy control populations was definitively associated with a demyelinating disease. Furthermore, this autoantibody could distinguish NMO from typical MS and was present in a large number of patients who suffered from optico-spinal MS, recurrent transverse myelitis, and other high-risk clinical syndromes. Because the antibody bound to a CNS water channel, it also raised the possibility that the antibody might be pathogenic and that NMO could be an autoimmune channelopathy. Although a pathogenic role for anti-AQP4 antibody is not proven, several lines of evidence suggest that AQP4 is a pathogenic target (Table 1).

A case report by Misu et al. [17•] of an acute NMO spinal cord lesion found diminished AQP4 staining by immunohistochemistry. Loss of AQP4 was found in central gray matter, particularly in a periventricular pattern where staining for glial fibrillary astrocytic protein (GFAP) was also substantially reduced. Furthermore, the periventricular areas characterized by loss of AQP4 and GFAP staining correspond to the areas where antibody and complement are known to deposit in NMO lesions [18]. In the areas surrounding the lesions, reactive gliosis with intense GFAP staining was present. Unlike AQP4 and GFAP, myelin basic protein staining was relatively preserved in the lesions. In contrast to the NMO case, spinal cord lesions from MS cases did not show loss of AQP4 and GFAP. The fact that tissue staining for GFAP was reduced and was lost for AQP4 in NMO spinal cord lesions suggests astrocytic podocytes could be degraded by anti-AQP4 autoantibodies and complement deposition. This study did not specify the stage of demyelination associated with the lesion, degree of astrocyte loss, or extent of tissue necrosis, factors that could confound the interpretation that AQP4 is targeted in NMO pathogenesis. It is also possible that AQP4 was endocytosed by astrocytes in response to the acute attack or that AQP4 staining was blocked by the presence of anti-AQP4 antibodies.

In a pathologic series of nine cases, Roemer et al. [19] further examined AQP4 immunohistochemical reactivity in MS and NMO lesions. In contrast to a stage-dependent loss of AQP4 in MS lesions, AQP4 was always lost in NMO lesions. Furthermore, the pattern of NMO loss corresponded to the pattern of IgG and complement deposition observed in NMO lesions. Interestingly, Roemer et al. [19] noted two types of NMO lesions. One type, seen primarily in optic nerve and spinal cord, was associated with inflammatory infiltrates, IgG and complement deposition, AQP4 loss, and demyelination. The second type, seen in the spinal cord and medulla, particularly the area postrema, showed inflammation, IgG and complement deposition, and AQP4 loss without demyelination. Based on this observation, Roemer et al. [19] concluded that AQP4 loss could occur independently of demyelination.

The observation of loss of AQP4 reactivity in the area postrema is particularly interesting because reversible T2 signal abnormalities were found on brain MRI studies of NMO patients who experienced intractable hiccups and vomiting [20]. It is possible that the reversible aspect of these symptoms and imaging findings associated with NMO plaques at this location are the consequence of autoantibody-mediated focal disruption of AQP4 function.

In a follow-up series to their case report, Misu et al. [21] found consistent loss of AQP4 in acute inflammatory NMO lesions without demyelination and also found loss of AQP4 in the majority of actively demyelinating lesions. However, in more chronic lesions, AQP4 staining could be detected regardless of whether demyelination accompanied the lesions. This observation correlates loss of AQP4 reactivity with the acute pathogenic process in NMO and suggests that loss of AQP4 reactivity may be reversible because of the return of AQP4 reactivity in chronic lesions. Loss of AQP4 reactivity independently in NMO spinal cord and optic nerve lesions was found by Sinclair et al. [22]. They also underscored the difference between NMO lesions that lost AQP4 reactivity and chronic MS lesions that showed increased gene expression of AQP4 and osteopontin.

Taken together, these pathologic studies have important implications for NMO. First, AQP4 appears to be targeted in acutely forming lesions by the anti-AQP4 antibody. Second, it appears that demyelination occurs after loss of AQP4 because acute spinal cord plaques show loss of AQP4 but preserved myelin basic protein reactivity [17•,21], whereas more chronic plaques show loss of both myelin basic protein and AQP4 [19]. It is not known whether loss of AQP4 function results in demyelination or whether demyelination occurs through other mechanisms. Third, depending on the lesion location, such as the area postrema, loss of AQP4 is associated with intense inflammation but apparently is uncoupled from demyelination.

Why spinal cord and optic nerve lesions in NMO are demyelinated is not immediately obvious from studies on AQP4. AQP4 localizes to the astrocytic podocytes surrounding nodes of Ranvier and paranode processes [23]. It is plausible that if the complement cascade is activated at these paranodal processes by NMO-IgG, then an inflammatory response could cause secondary injury to oligodendroglial cells that are in contact with the astrocytes. Alternatively, axonal injury at the nodes of Ranvier could result in secondary demyelination. Glutamate toxicity could also contribute to injury in NMO because expression of the astrocytic glutamate transporter GLT1 is in part dependent on the presence of AQP4 [24]. Thus, it is possible that oligodendroglial cells might be susceptible to focal increases in glutamate concentration as a consequence of downregulation of astrocytic AQP4 by the anti-AQP4 antibody [23].

The NMO autoantibody is an IgG subclass I antibody and is capable of fixing complement. Hinson et al. [23] sought to understand the pathogenic potential of the AQP4 autoantibody by studying the effects of antibody binding to AQP4-transfected HEK cells. First, they showed that anti-AQP4 antibodies from NMO patient sera bound to the extracellular domain of AQP4. Second, they showed that binding of anti-AQP4 antibodies resulted in the rapid endocytosis of AQP4, which subsequently formed large cytoplasmic aggregates. Interestingly, removal of anti-AQP4 serum was followed by redistribution of AQP4 to the cell surface, implying reversibility of AQP4 loss under some conditions. Third, they showed that anti-AQP4 serum could cause C9neo complement deposition on cell membranes and mediate cell lysis. This process was found to be specific for anti–AQP4-IgG antibodies and not for anti–AQP4-IgM antibodies. Taken together, these studies show that anti-AQP4 antibody can cause endocytosis of AQP4 from plasma membranes and can fix complement, causing cell lysis. An important caveat to these in vitro observations is that the studies were performed on transfected HEK cells; it is not known whether anti-AQP4 antibodies have in vivo effects on astrocytes. Nevertheless, the implication is that anti-AQP4 antibodies could have direct pathogenic effects on AQP4, thereby explaining the loss of AQP4 reactivity from NMO lesions.

Because the AQP4 water channel is expressed ubiquitously in astrocytes, it is perhaps difficult to understand restriction of NMO for the optic nerves and spinal cord. With the revised NMO diagnostic criteria, it became clear that brain MRI lesions were present in up to 50% of individuals with anti-AQP4 antibody [25]. Most of these lesions were nonspecific; however, 10% were similar to lesions seen in MS whereas 5% had cerebral, brainstem, or diencephalic involvement that was unusual for MS. Interestingly, hypothalamic and periventricular lesions in NMO correspond to areas of high AQP4 expression [26]. Although many brain lesions in NMO are asymptomatic, hypothalamic involvement in NMO was associated with endocrinopathies [27–30.] It is not known why brain lesions in NMO are often asymptomatic, whereas spinal cord and optic nerve lesions are rarely, if ever, asymptomatic. Furthermore, NMO brain lesions that are hyperintense on T2-weighted imaging are typically not hypointense on T1-weighted imaging and often resolve over time [31]. It is possible that such lesions could correspond to a more transient pathologic process, such as edema, rather than demyelination. Thus, asymptomatic lesions may be associated with temporary loss of AQP4 without demyelination, whereas symptomatic lesions could be associated with both loss of AQP4 and demyelination.

Proof that anti-AQP4 antibodies are directly pathogenic will require adoptive transfer experiments in animal models of NMO. To date, a convincing model of NMO has not been developed. One study found that immunization with AQP4 peptides in mice treated with lipopolysaccharide could induce four-limb motor impairment [32]. Although human anti-AQP4 antibodies recognize murine AQP4, these antibodies would not be expected to fix complement in mice because of incompatibility between the human Fc gammaglobulin chain and murine complement. Transfected mouse plasma cells with chimeric monoclonal antibodies that have the human antibody–binding domains spliced to the murine Fc portion of the IgG have the potential to show a direct pathogenic effect. Similarly, purified human anti-AQP4 chimeric mouse antibodies could be tested for direct pathogenic effects by peripheral infusion. Such experiments have yet to be performed.

It seems likely that the pathologic process in NMO is more complex than complement-mediated tissue injury caused by anti-AQP4 antibodies. That at least one of four NMO cases are not seropositive for anti-AQP4 antibodies demonstrates that the clinical manifestations of NMO can occur completely independently of the anti-AQP4 antibody. It is possible that other autoantibodies may be involved in such cases. Indeed, a pilot study found three novel autoantibodies in a case of NMO [33]. One of these antibodies directed against cleavage and polyadenylation specificity factor 73 declined following treatment with rituximab. Although potentially interesting, whether there is a relationship between this or other autoantibodies and NMO is speculative.

NMO Treatment

NMO's association with AQP4 antibodies and the fact that these antibodies might participate in NMO pathogenesis by depleting AQP4 from astrocytes suggests that NMO is at least in part a humorally mediated disease. Treatment of acute attacks of NMO supports this hypothesis. Based on the experience in MS, high-dose glucocorticoids are the primary therapy for acute attacks of transverse myelitis and optic neuritis in NMO. Unfortunately, NMO attacks often only partially respond, or do not respond at all, to treatment with glucocorticoids. In this setting, plasmapheresis is often used. A randomized, sham-controlled trial of plasma

exchange in glucocorticoid-refractory CNS demyelinating diseases included two cases of NMO [34]. One NMO patient who received active plasma exchanges experienced a positive response to treatment whereas the other patient who received sham exchange did not. A retrospective case series of plasmapheresis used to treat glucocorticoid-refractory severe attacks of CNS demyelination in MS, NMO, and transverse myelitis found a marked or moderate improvement in 60% of NMO patients [35]. A study of six anti-AQP4 seropositive patients who suffered from glucocorticoid-refractory attacks found moderate clinical improvement in three cases following plasmapheresis treatment. The clinical response was brisk in these cases, with onset of improvement following the first or second exchange [36]. Two case reports also describe benefit for lymphocytapheresis [37,38].

Maintenance of remission in NMO is challenging. Disability in NMO is largely caused by severe attacks of demyelination. Unlike MS, only some NMO patients develop secondary progressive changes [39]. Thus preventing attacks in NMO may prevent cumulative disability. Anecdotal experience found that NMO does not respond to immunomodulatory therapy [10]. A multicenter, retrospective case series of 26 patients found that NMO patients (n = 19) treated with immune suppression were less likely to relapse than NMO patients treated with interferon (n = 7) [40]. All seven (100%) of the interferon-treated patients relapsed by 12 months, whereas only 25% of immune suppressive–treated patients relapsed by 36 months. Indeed, one study suggested that interferon β-1b treatment increased relapses in Japanese optico-spinal MS patients [41]. The optico-spinal MS patients in this study were not assessed for anti-AQP4 seropositivity; however, their clinical features were more consistent with NMO (longitudinally extensive spinal cord lesions, severe optic nerve injury, and cerebrospinal fluid pleocytosis).

Several case series suggest that immune suppression may prevent relapses in NMO. The first of these studies, conducted by Mandler et al. [42], used combined treatment of azathioprine and prednisone in seven newly diagnosed NMO patients (two attacks). Azathioprine is a broad-spectrum immune suppressant and is approved by the US Food and Drug Administration (FDA) for renal transplant rejection and severe rheumatoid arthritis. Serious complications of azathioprine treatment include myelosuppression, lymphoma, malignancies, hepatotoxicity, and opportunistic infections. During 18 months of follow-up, no patients experienced further relapses and the median Expanded Disability Status Score gradually declined. Based on this series, azathioprine plus prednisone became the standard of care in NMO patients. Unfortunately, some patients continue to suffer from relapses despite treatment with azathioprine and prednisone.

Rituximab was also used in treatment-refractory NMO cases [43•]. Rituximab is a monoclonal antibody directed against CD20, a cell surface marker expressed on pre-B and B cells. Rituximab causes depletion of B cells and is FDA approved for treatment of non-Hodgkin's lymphoma and rheumatoid arthritis. Because several lines of evidence suggest that NMO is at least in part a humorally mediated disease, B-cell depletion in NMO might be expected to be beneficial. Serious complications of rituximab included severe and even fatal infusion reactions, hepatitis, new or reactivated viral infections, and progressive multifocal leukoencephalopathy. In this open-label case series, seven of eight NMO patients experienced a substantial reduction in relapsing activity following rituximab treatment, with a compensatory improvement in neurologic function. A retrospective follow-up study of 26 patients [44] and preliminary results from an open-label clinical trial of 20 NMO patients [45] found similar results. Some patients with very aggressive disease do not appear to respond immediately to treatment with rituximab, indicating that if rituximab has benefit in NMO, its effects may not be immediate [46].

Mitoxantrone has also been used to treat NMO [47•]. Mitoxantrone is a broad-spectrum immunosuppressant and is FDA approved for treatment of MS, acute myeloid leukemia, and symptomatic hormone-refractory prostate cancer. Known serious adverse reactions include leukemia, cardiotoxicity, hepatotoxicity, myelosuppression, ovarian failure, and infections. In an open-label case series of five NMO patients treated with mitoxantrone, three of them did not experience relapses during the average follow-up time of 13 months. Although a statistical analysis was not performed, the investigators noted clinical and radiographic improvement in mitoxantrone-treated NMO patients. To date, mitoxantrone is the only medication that may be beneficial in NMO that is FDA approved for MS.

A retrospective case series of nine NMO patients compared the annualized relapse rates for each patient during periods when they received or did not receive daily glucocorticoids [48]. Relapse rates were significantly lower during periods when patients were treated with at least 10 mg/d of prednisone. The investigators suggested that daily glucocorticoids could be beneficial in preventing NMO relapses [48]. Because daily glucocorticoid treatment was typically initiated in response to ongoing disease activity, it is not clear whether the purported treatment response reflects a change in the disease activity because of disease duration or a treatment effect. Some NMO patients become glucocorticoid dependent; nevertheless, daily glucocorticoids are inexpensive and have the potential to be combined with other immune-suppressing therapies. Two case reports also suggested that intravenous immunoglobulin may be beneficial in preventing NMO relapses [49,50].

Conclusions

The identification of NMO-IgG as a biomarker for NMO is of proven diagnostic value. In the setting of diagnostic uncertainty, a seropositive test for anti-AQP4 can be

very helpful for prognosis and potentially for selecting treatment options. Because the biomarker is an autoantibody targeting AQP4 (a water channel abundant on astrocytic podocytes), it raises the possibility that NMO is a humorally mediated disease. Indeed, AQP4 appears to be lost from acute NMO lesions. Anti-AQP4 antibodies can fix complement and cause cell lysis in an in vitro–transfected AQP4 expression system. Despite these advances, many unanswered questions remain. Proof that anti-AQP4 antibodies cause disease is lacking, and convincing animal models have not been developed. Why NMO has a predilection for the optic nerves and spinal cord is hard to explain given the ubiquitous expression of AQP4. Furthermore, neither the link between AQP4 loss and demyelination nor the striking inflammation seen in NMO is readily explained by anti-AQP4 antibodies. Indeed, it seems more likely that vigorous inflammation is needed initially in order to expose astrocytic targets to anti-AQP4 antibodies. Lastly, the fundamental cause of the presumed auto-immunity in NMO remains elusive. In this regard, NMO is very similar to MS.

Disclosure

Dr. Cree has received a grant from Genentech for a clinical trial of rituximab in NMO.

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