

The aetiology of AQP4 antibody production in Neuromyelitis optica spectrum disorder

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INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an antibody-mediated autoimmune disease that targets astrocytes in the central nervous system (CNS).¹ Despite the well-established role of AQP4 antibodies in NMOSD, the underlying aetiology driving their production remain poorly understood. We aimed to identify demographic, biological, and regional factors influencing aquaporin-4 (AQP4) antibody titers in NMOSD.

METHODS

A retrospective analysis was conducted on AQP4 antibody titers in 3,915 NMOSD patients using a unified and a standardized assay. Variations in antibody levels were assessed across sex, age, and region, with statistical analyses evaluating their impact on AQP4 antibody production.

RESULTS

Female sex emerged as the primary determinant of AQP4 antibody positivity and titers, with females exhibiting significantly higher antibody levels than males. Logistic regression analysis indicated that females have a significantly increased risk of high-titer AQP4 antibodies (OR = 1.63, 95% CI: 1.32–2.01). Age-related peaks in antibody titers were observed in females in the 29–40 and 52–62 age groups, correlating with reproductive and menopausal phases, respectively, suggesting hormonal fluctuations as key modulators of antibody production. Elevated antibody titers were also noted in females during early childhood (<12 years) and advanced age (>63 years), which may be attributed to X-linked genetic factors (Figure 1). Serum antibody titers generally surpassed cerebrospinal fluid (CSF) titers, except in 23 patients with elevated CSF levels, indicating potential intrathecal synthesis. CSF titers showed a positive correlation with age, particularly at titers exceeding 1:32 (Figure 2). Regional analysis revealed a higher prevalence of AQP4 antibody positivity and a greater female-to-male ratio in southeastern coastal regions of China. Among cities,

Jiangsu exhibited the highest proportion of women with high-titer AQP4 antibodies (>1:1000), while Shanghai had the lowest. Despite being at similar latitudes, hepatitis B virus infection rates were substantially higher in Jiangsu (16.7 per 100,000) compared to Shanghai (1.2 per 100,000), suggesting that regional environmental factors, particularly infectious agents, may interact with sex and contribute to higher antibody titers (Figure 3).

Figure 1. Characteristics of 3797 AQP4-IgG-seropositive NMOSD patients.

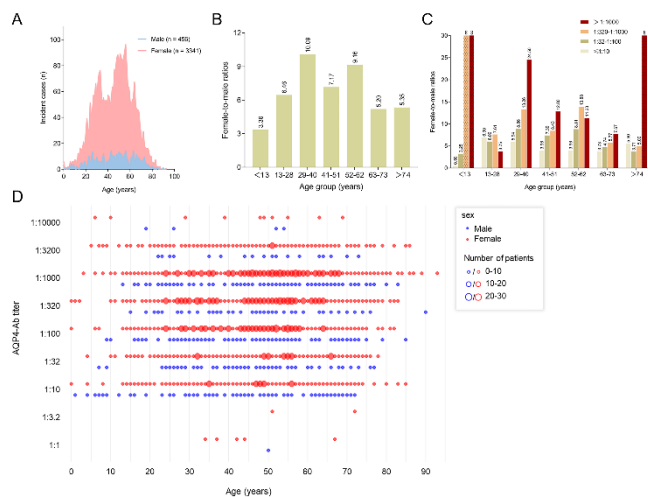


Figure 2. AQP4-IgG profiles in cerebrospinal fluid (CSF) of NMOSD Patients.

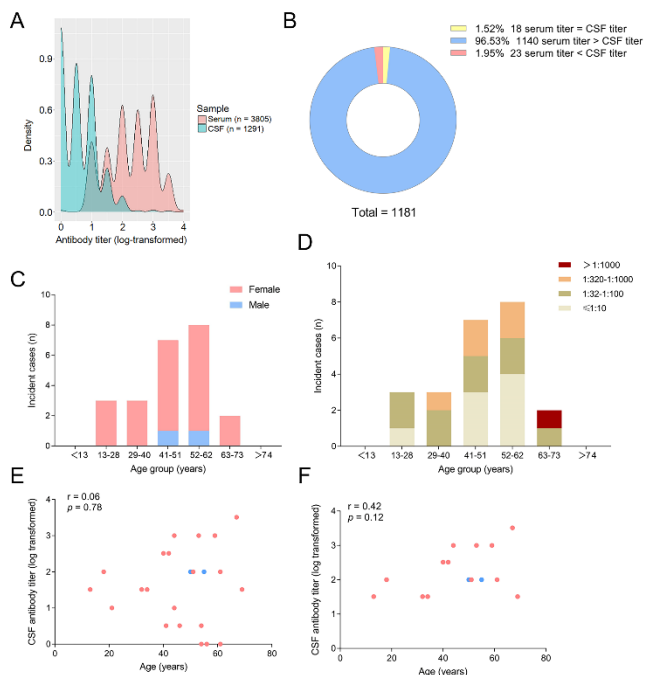
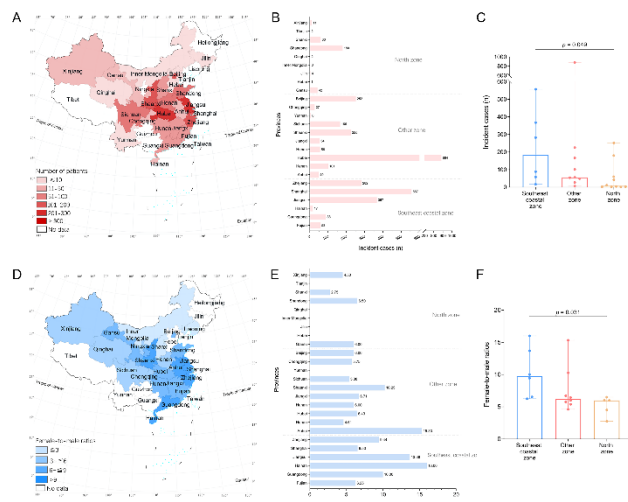


Figure 3 Spatial distribution patterns of AQP4 antibodies in NMOSD across China.



DISCUSSION

AQP4 antibody production is primarily influenced by sex, with women at greater risk for high-titer antibodies. Age-related hormonal changes and regional environmental factors act as interacting influences, particularly in females, contributing to NMOSD onset and progression. These findings provide insights for future research and targeted interventions.

LITERATURE

1. Jarius S, Paul F, Weinshenker BG, Levy M, Kim HJ, Wildemann B. Neuromyelitis optica. *Nat Rev Dis Primers*. Oct 22 2020;6(1):85. doi:10.1038/s41572-020-0214-9