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Pathological analysis of the deposition of IL-6 in the central nervous tissues in Neuromyelitis Optica Spectrum Disorders

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Background

Neuromyelitis Optica Spectrum Disorders (NMOSD) is an astrocytopathic disease associated with anti-aquaporin-4 (AQP4) antibody. Interleukin-6 (IL-6) contributes to the production of AQP4 antibody[1], and CSF-IL-6 levels are markedly elevated in NMOSD[2-4]. Additionally, recent clinical trials revealed that IL-6 receptor inhibitors are effective in preventing relapse of NMOSD[4-7]. However, the pathogenic role of IL-6 in the central nervous tissues of NMOSD remains unclear.

Objective

To clarify the deposition of IL-6 in the central nervous tissues in NMOSD and the possible pathogenetic implications.

Materials and Methods

With immunohistochemical techniques, we examined staining pattern of IL-6 in the different stages of astrocytopathic lesions in 18 autopsied cases of NMOSD.

Results

The onset age was 54.5 years (median, range 14-79), and the disease duration was 22.5 months (0.6-324). IL-6 was mainly detected at fibers in the perivascular space, pia matter and tissues surrounding astrocytopathic lesions, in 86% (25/29 lesions) of acute lesions and in 24% (8/33 lesions) of chronic ones. In particular, in the acute lesions with active complement deposition, IL-6 was often seen at the perivascular areas (74% in perivascular areas, 32% in pia matter, 5% in surrounding tissues), while in the subacute lesions, IL-6 was commonly deposited at surrounding tissues of asctocytopathic lesions (18% in perivascular areas, 9% in pia matter, 82% in surrounding tissues). IL-6 deposition was not seen outside of the astrocytopathic lesions. Interestingly, the expression pattern of IL-6 receptor was very similar to that of IL-6.

【Talbe-1. Summary of clinical presentation】

Pt	age at onset, yr	sex	disease duration, mo	period from last onset, mo	AQP4 antibody positivity	Pathological Staging
1	78	F	2	0.5	+	Acute
2	63	M	0.75	0.75	+	Acute
3	57	M	8	0.5	+	Acute~Subacute
4	53	F	3	2	+	Acute~Subacute
5	46	F	252	12	+	Chronic
6	71	F	120	36	+	Chronic
7	56	F	228	108	+	Chronic
8	46	F	156	108	+	Chronic
9	35	F	132	NA	NA	Acute~Chronic
10	43	F	240	NA	NA	Acute~Chronic
11	39	M	144	12	NA	Acute~Chronic
12	79	M	9	NA	NA	Subacute~Chronic
13	66	F	12	0.75	NA	Acute~Chronic
14	77	M	3	3	NA	Subacute~Chronic
15	65	F	28	6	NA	Subacute~Chronic
16	50	F	21	NA	NA	Chronic
17	14	F	60	2	NA	Chronic
18	38	F	324	4	NA	Chronic

Pt: patient, yr: year, mo: month, AQP4: aquaporin4, F: female, M: male, NA not applicable

【Figure-3. Relationship between the staining pattern of IL-6 and the pathological stage of astrocyte】

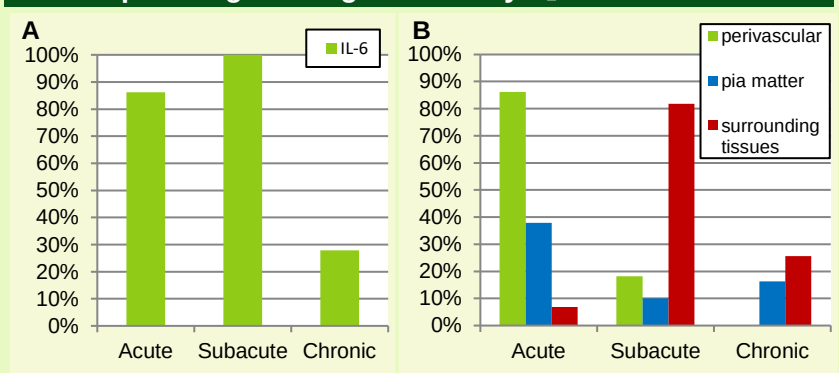

Figure-3. Relationship between the staining pattern of IL-6 and the pathological stage of astrocyte. (A) IL-6 was observed in 86% (25/29 lesions) of acute, 100% (11/11 lesions) of subacute and 28% (12/43 lesions) of chronic lesions defined by the astrocytopathy staging. (B) In the acute lesions, IL-6 was predominantly deposited at the perivascular areas (86% perivascular, 38% pia matter, 7% surrounding tissues), while in the subacute and chronic lesions, mainly detected in the surrounding tissues of asctocytepathic lesions (subacute lesions: 18% perivascular, 9% pia matter, 82% surrounding tissues, chronic lesions: 0% perivascular, 16% pia matter, 26% surrounding tissues).

【Figure-1. IL-6 deposition in acute NMOSD lesions】

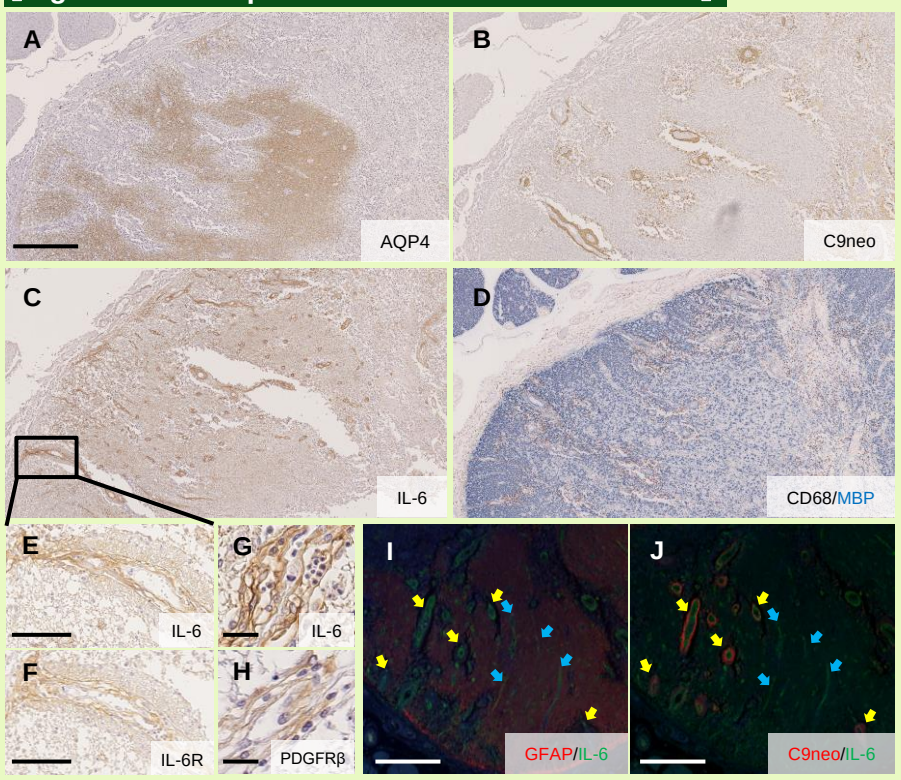

Figure-1. IL-6 expression in acute NMOSD lesions. (A-J) Acute astrocytopathic lesion of spinal cord in patient 9. A-D represented the same area. Perivascular AQP4-loss lesions (A) with activated complement depositions (B) and relatively preserved myelin sheaths (D) indicated acute NMOSD lesion. A lot of vessels located in these lesions were accompanied by IL-6 deposition (C) at perivascular area and pia matter (scale bar = 500μm). (E) High-magnification images of a selected area indicated by the rectangle in C. IL-6 was seen in fibrous structures in the perivascular space (E and G). This staining pattern is quite similar to that of IL-6R (F) and pericyte marker PDGFRβ (H) (scale bar = 100μm in E and F, 25μm in G and H). (I-J) Fluorescence double staining of IL-6 (green) and GFAP (I, red) or C9neo (J, red). IL-6 staining of perivascular area was found not only in astrocyte destructive lesions with complement deposition (yellow arrow), but also the area where astrocytes are not impaired (blue arrow) (scale bar = 500μm).
AQP4: aquaporin4, GFAP: glial fibrillary acidic protein, IL-6: interleukin-6, MBP: myelin basic protein, PDGFR: Platelet-Derived Growth Factor.

【Figure-2. IL-6 deposition in subacute NMOSD lesions】

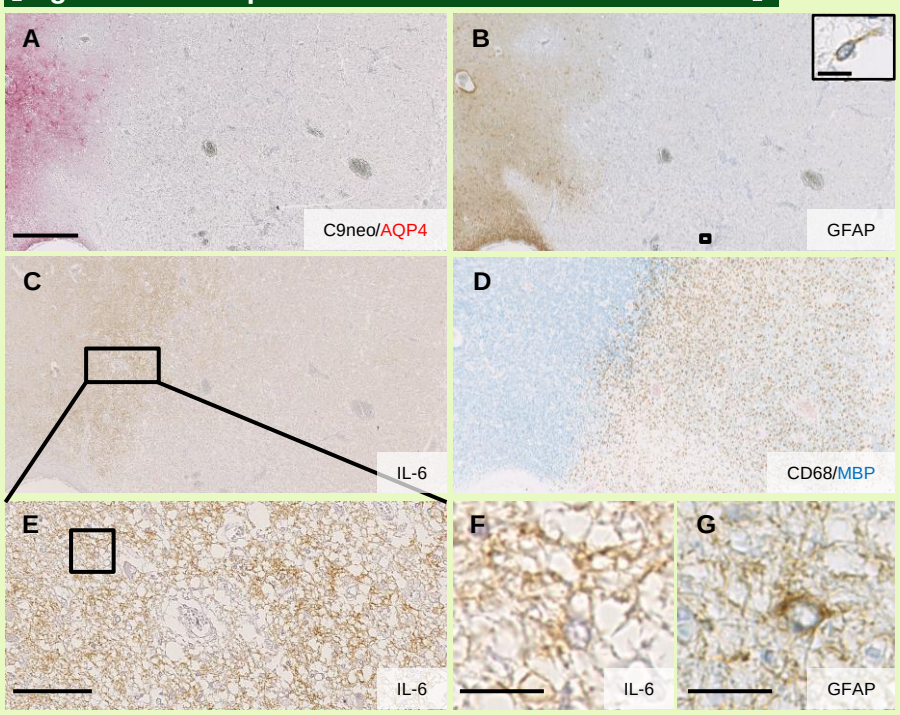

Figure-2. IL-6 expression in subacute NMOSD lesions. (A-G) Subacute astrocytopathic lesion of pons in patient 4. A-D represented the same area. Widely loss of AQP4 lesions without complement depositions (A) where contain immatured progenitor cells of astrocytes (B) with evident demyelination (D) indicated subacute NMOSD lesion. Staining of IL-6 was seen at edge of the AQP4-loss lesions (C) (scale bar = 500μm or 10μm in insert of B). (E) High-magnification images of a selected area indicated by the rectangle in C. IL-6 is stained in a fibrous tissue similar to astrocytes (scale bar = 100μm). (F) Further enlarged image of a selected area indicated by the rectangle in E. Staining pattern of IL-6 (F) is similar to that of GFAP staining (G) (scale bar = 20μm).
AQP4: aquaporin4, GFAP: glial fibrillary acidic protein, IL-6: interleukin-6, MBP: myelin basic protein.

Conclusion

Our study showed that IL-6 deposition spread from the perivascular space to surrounding tissues of NMOSD lesions as time proceeded, suggesting that IL-6 may contribute to the lesion development.

<reference>
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