研究成果の刊行に関する一覧表

(2012年4月1日～2015年3月31日迄)

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英文著書　：11ポイント・Century

日本文著書　：11ポイント・MS明朝

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hagiwara K, Ogata K, Okamoto T, Uehara T, Hironaga N, Shigeto H, Kira J, Tobimatsu S.	Age-related changes across the primary and secondary somatosensory areas: an analysis of neuromagnetic oscillatory activities	Clinical Neurophysiology	125	1021-9	2014

研究成果の刊行に関する一覧表
(2012年4月1日～2015年3月31日迄)

書　籍　　御名前：　楠　進　先生

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著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
なし							

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なし					

研究成果の刊行に関する一覧表

書 籍 名前： 吉田 眞理 なし

雑 誌 名前：吉田 眞理

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yoshida M	Astrocytic inclusions in progressive supranuclear palsy and corticobasal degeneration.	Neuropathology.	34	555-570	2014
Tatsumi S, Uchihara T, Aiba I, Iwasaki Y, Mimuro M, Takahashi R, Yoshida M.	Ultrastructural differences in pretangles between Alzheimer disease and corticobasal degeneration revealed by comparative light and electron microscopy.	Acta Neuropathologica Communications	2	161	2014
Yonekawa T, Murai H, Utsuki S, Matsushita T, Masaki K, Isobe N, Yamasaki R, Yoshida M, Kusunoki S, Sakata K, Fujii K, Kira JI.	A nationwide survey of hypertrophic pachymeningitis in Japan.	J Neurol Neurosurg Psychiatry	85	732-9	2013
Riku Y, Ikeuchi T, Yoshino H, Mimuro M, Mano K, Goto Y, Hattori N, Sobue G, Yoshida M.	Extensive aggregation of α-synuclein and tau in juvenile-onset neuroaxonal dystrophy: an autopsied individual with a novel mutation in	Acta Neuropathol Commun.	1	12	2013

	the PLA2G6 gene-splicing site.				

平成25年度　研究成果の刊行に関する一覧表

雑誌	御名前　星野　友昭先生

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Oda H, et al.	IL-18 expression, CD8+ T cells and eosinophils in lungs of non-smokers with fatal asthma.	Annals of Allergy, Asthma and Immunology	112	23-28.e1	2014
Yokota-Nakatsuma A, et al.	Retinoic acid prevents mesenteric lymph node dendritic cells from inducing IL-13-producing inflammatory Th2 cells.	Mucosal Immunol	7	786-801	2014
Yamada K, et al.	Feasibility re-evaluation of 75 mg/m(2) docetaxel in Japanese patients with previously treated non-small cell lung cancer.	Jpn J Clin Oncol	44	338-345	2014
Takeoka H, et al.	The progression of comorbidity in IL-18 transgenic chronic obstructive pulmonary disease mice model.	Biochem Biophys Res Commun	445	597-601	2014
Suetomo M, et al.	COPD assessment tests scores are associated with exacerbated chronic obstructive pulmonary disease in Japanese patients.	Respir Investig	52	288-295	2014
Kaku Y, et al.	Overexpression of CD163, CD204 and CD206 on alveolar macrophages in the lungs of patients with severe chronic obstructive pulmonary disease.	PLoS One	9	e87400	2014
Kaieda S, et al.	An autopsy case of refractory vasculo-Behcet's disease.	Mod Rheumatol			2014
Kaieda S, et al.	Successful treatment of rectal ulcers in a patient with systemic lupus erythematosus using corticosteroids and tacrolimus.	Mod Rheumatol	24	357-360	2014
Ishii H, et al.	Predictive factors in patients with EGFR mutation-negative non-small cell lung cancer treated with erlotinib.	Oncol Lett	8	2699-2704	2014
Ishii H, et al.	Significance of programmed cell death-ligand 1 expression and its association with survival in patients with small cell lung cancer.	J Thorac Oncol			2014
Azuma K,, et al.	Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer.	Ann Oncol	25	1935-1940	2014
Azuma K,, et al.	Humoral immune responses to EGFR-derived peptides predict progression-free and overall survival of non-small cell lung cancer patients receiving gefitinib.	PLoS One	9	e86667	2014
Azuma K,, et al.	FGFR1 activation is an escape mechanism in human lung cancer cells resistant to afatinib, a pan-EGFR family kinase inhibitor.	Oncotarget	5	5908-5919	2014

V　脱髄性疾患，遺伝性ニューロパチー

中枢性脱髄疾患

アトピー性脊髄炎

Atopic myelitis

山﨑　亮[1]
吉良潤一[2]

Key words：アトピー素因，好酸球性脊髄炎，ミクログリア，血漿交換

1. 概念・定義

アトピー性脊髄炎とは，アトピー性皮膚炎，気管支喘息，アレルギー性鼻炎・結膜炎などのアトピー素因を有する患者でみられる脊髄炎である．1997年に吉良らが，4例の高IgE血症とアトピー性皮膚炎を伴った，四肢の異常感覚（じんじん感）を呈し頸髄後索を主病変とする脊髄炎を報告し，アトピー性脊髄炎と命名した[1]．

2003年に小副川らが全国調査を行った際の暫定的な疾患定義は，‘ダニ特異的IgEを含む高IgE血症を認め，アトピー性疾患を併発している原因不明の脊髄炎’であった[2]．その後，症例の蓄積で新たに診断基準が策定された（**表1**）[3]．現在の診断基準は，①原因不明の脊髄炎，②抗原特異的IgE陽性，③Barkhofの多発性硬化症における脳MRI診断基準に合致する病変を認めない，の3項目を絶対基準とするもので，これに病理基準や相対基準を合わせて確定診断および推定診断が可能である．

2. 疫　学

アトピー性脊髄炎の全国調査は，小副川ら（2000-01年）[2]と磯部ら（2006-07年）[4]によって行われた．現在の我が国における推定患者数は約1,000人で男性に多い傾向があり，平均発症年齢は35歳であった．脊髄炎発症に先行したアトピー性疾患は約7割に認め，そのうちアトピー性皮膚炎が45％と最も多く，アレルギー性鼻炎（43％），気管支喘息（30％），食物アレルギー（16％）の順であった．そのほかの臨床症状および検査所見は後述するが，現在までに明らかな有病率の地域差は認められない．また，本疾患は海外からも報告がある[5,6]が，症例数が少ないので有病率や臨床症状の人種差に関しても今後の検討課題となっている．

3. 病　因

アトピー性脊髄炎の発症メカニズムは不明である．疾患の定義であるアトピー素因の存在や高IgE血症から考えると，ヘルパーT細胞のThバランスは末梢において主にTh2に偏っていると思われる．すなわち，Th2細胞のシグナルは形質細胞からのIgE産生を促進．これにより肥満細胞からヒスタミンなどが遊離し，血管透過性の亢進をきたす．また，Th2は末梢血好酸球も活性化・増殖させる．末梢組織で増殖したTh2細胞は脳脊髄液腔へ侵入し，準備状態となる．実際の患者髄液中ではIL-9とCCL11（eotaxin-1）の増加がみられる[7]．CCL11は好酸球上のCCR3およびCCR5と結合し細胞遊走因子として働き，IL-9はTh2からTh9への分化を誘導すると考えられている．Th9細胞はCCL11やIL-9の放出によって好酸球の遊走や増殖などに関与している可能性がある．

一方，中枢神経ではアトピー性疾患に伴ってミクログリアという脳実質内常在グリア細胞が活性化している．当研究室では，卵アルブミン

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表1 アトピー性脊髄炎 新診断基準(文献[3]より引用)

絶対基準	以下の3項目をすべて満たす 1) 原因不明の脊髄炎 2) 抗原特異的IgE陽性 3) Barkhofの脳MRIによる多発性硬化症診断基準 (①1造影病変もしくは9傍皮質病変, ②1テント下病変, ③3脳室周囲病変)をすべて満たさない
病理基準	脊髄生検組織で, 血管周囲リンパ球浸潤や好酸球の浸潤を認め, 肉芽腫を伴うこともある
相対基準	1) 現在または過去のアトピー性疾患歴 2) 高IgE血症(>240 U/mL) 3) 髄液中IL-9(>14.0 pg/mL)もしくはCCL11(>2.2 pg/mL) 4) オリゴクローナルバンド(OCB)なし
確定診断	1) 絶対基準+病理基準 2) 絶対基準+相対基準2項目以上+(4)(OCBなし)
推定診断	1) 絶対基準+相対基準1項目以上+(4)(OCBなし) 2) 絶対基準+相対基準2項目以上

(OVA)感作マウスの中枢神経系において, OVAの腹腔内注射後3週の脊髄ミクログリアの活性化を認めている. この活性化は後角に強いので, 何らかの感覚性入力が末梢感覚神経の過剰興奮を誘発し, 反応性にミクログリアが活性化している可能性が高い. 実験的自己免疫性脳脊髄炎(EAE)モデルマウスでは, 脊髄後根神経節からのシグナルが交感神経節の刺激を介して血管内皮のCCL20高発現を誘導し, 後索への病原性Th17細胞の脊髄浸潤を促すとの報告もあることから[8], アトピー性脊髄炎における頸髄後索病変の形成にもこのような感覚神経の異常活性化に伴うグリア炎症が関与している可能性が高い. また, CCL20の受容体であるCCR6は主にT細胞, B細胞および樹状細胞に発現しているが, 好酸球にも発現している[9]ことから, このような刺激が好酸球の脊髄浸潤に直接寄与している可能性もある.

これらの中枢および末梢双方における炎症準備状態から, 何らかのきっかけにより中枢神経内への炎症細胞浸潤が惹起され, 好酸球性炎症による組織破壊に至ると考えられる.

4. 病　　態

アトピー性脊髄炎は, 基礎となるアトピー性疾患の増悪後に発症する傾向がある. 発症様式は急性, 亜急性, 慢性それぞれ3割で, 単相性経過は3割, あとの7割は動揺性に慢性の経過をたどる. 初発症状は7割で四肢遠位部の異常感覚(じんじん感)や感覚鈍麻で, 運動障害も6割にみられるが軽症であることが多い. 深部反射は8割で亢進し, 排尿障害を伴うこともある.

MRIでは, 6割以上の症例で頸髄後索にGd造影効果を伴う病変を認める(**図1**). 一方大脳病変を認める症例は1割に満たない. 電気生理学的検査では, 潜在性の末梢神経障害を1/4の症例で認め, 運動神経誘発電位(MEP)や感覚神経誘発電位(SEP)では中枢性の障害を認める. 血液検査では高IgE血症を9割に認め, 高好酸球血症も6割に認める. 髄液検査では1/4の症例で軽度の細胞数増多を認めるが好酸球はみられない. また, 髄液中のIL-9とCCL11(eotaxin-1)の増加がみられるが, 多発性硬化症などでしばしば高値であるIL-17やIFNγは本疾患では増加していないのも特徴である[3].

その非特異的なMRI所見から, 脊髄腫瘍な

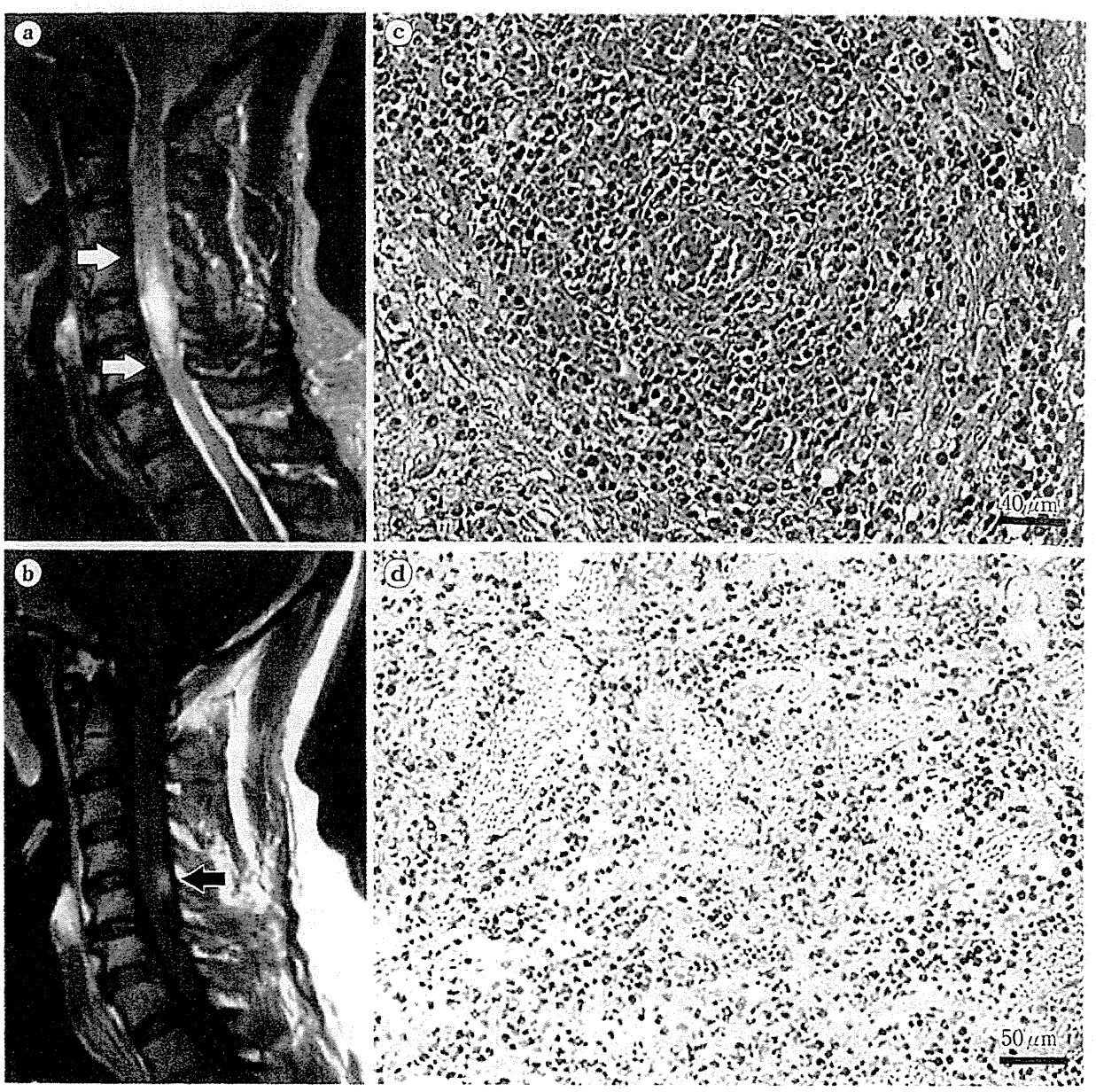

図1　アトピー性脊髄炎のMRIと病理組織所見(文献[10]より引用)

a. 53歳男性患者のMRI T2強調画像：C4-6にT2延長病変を認める(白矢印). b. aと同部位のガドリニウム造影T1強調画像：C5/6に造影病変を認める(黒矢印). c. 同患者の生検組織画像：小静脈周囲に多数の好酸球浸潤を認める. ヘマトキシリン-エオジン染色. d. 同患者の生検組織画像：著明なECPの沈着を認める(褐色). 抗ECP抗体染色.

どとの鑑別のため生検を施行される場合があるが，本疾患では病理学的に血管周囲の好酸球を主とした炎症細胞浸潤，髄鞘や軸索の破壊がみられる．またeosinophil cationic protein(ECP)の沈着がみられ，好酸球由来のタンパクによる組織破壊が示唆される(**図1**)．また，疾患急性期にはCD4陽性T細胞がみられるが，慢性期にはCD8陽性T細胞が多く認められ，これらの細胞傷害性T細胞も組織破壊の原因の一つと考えられる[10]．

5. 診断と鑑別診断

臨床的に，アトピー素因があり，四肢の異常感覚を訴える若年患者を診た際には，アトピー性脊髄炎も鑑別対象となる．

前述のように，疾患の診断は近年策定された

新診断基準と照合することで比較的容易に行うことができる[3]．鑑別すべき疾患としては，頸椎症などに伴う頸髄の圧迫性病変，多発性硬化症，視神経脊髄炎，腫瘍性病変，各種感染症(寄生虫，真菌，ウイルス，細菌)に関連した脊髄炎(HTLV-1関連脊髄症や神経梅毒など)，膠原病，サルコイドーシス，脊髄血管奇形，放射性脊髄炎などが挙げられる．寄生虫性脊髄炎は，アトピー性脊髄炎同様に高IgE血症や好酸球増多を認めるため，鑑別診断として重要である．また，同じくアレルギー性機序で末梢神経障害を呈するChurg-Strauss症候群(CSS)(別名：アレルギー性肉芽腫性血管炎，allergic granulomatous angiitis)も重要な鑑別対象である．CSSは気管支喘息やアレルギー性鼻炎に引き続いて末梢血好酸球増多を伴う血管炎を生じ，末梢神経炎や消化管潰瘍，脳梗塞・脳出血，腎機能障害などの多臓器障害をきたす．30-60歳代に発症するため発症年齢も類似している．CSSでは抗好中球細胞質抗体(MPO-ANCA)が約半数で陽性となるが，アトピー性脊髄炎では陰性である．また，CSSでは脳神経系以外の病変を認めることもアトピー性脊髄炎との鑑別点となる[4]．しかしながら，好酸球性炎症に伴う臓器障害という点は酷似しており，少なくとも一部はオーバーラップしている症例も存在していると考えられており，今後の症例蓄積が待たれる．

6. 治療と予後

村井ら[11]によるアトピー性脊髄炎患者26例の治療効果の検討では，副腎皮質ステロイド(CS)治療のみ，もしくは免疫グロブリン静注療法(IVIg)のみではそれぞれ72％，60％の患者で臨床症状の改善がみられた．一方血漿交換(PE)は単独でも9割の患者で臨床症状の改善がみられ，ほかの治療と比較し有意に効果的であった．第2回全国調査では6割でCS治療が行われており，PEは25％で施行されたにすぎなかったが，そのうち8割で有効であった．PEは本疾患の治療としてまだ一般的ではないが，CS治療に反応しない症例にはPEを積極的に施行すべきである．本疾患の予後は，発症から6.6年後の総合障害度評価尺度(EDSS)スコア(10段階評価で10点が最重症)で平均2.3点程度の障害が残るのみで，一般的に大きな障害を残しにくい[4]．

また，本疾患は多発性硬化症との鑑別がしばしば問題となるが，多発性硬化症の治療に用いられるインターフェロンβ(IFN-β)や，現在開発中のグラチラマー酢酸塩(glatiramer acetate)は，Th2タイプのT細胞を活性化させ，好酸球性炎症を悪化させる可能性が高いため勧められない[3]．治療法選択という観点からも多発性硬化症との鑑別は非常に重要である．また，本疾患の再発予防のため，基礎となるアトピー素因の治療は非常に重要である．

おわりに

近年の食生活の欧米化や生活環境の変化に伴い，アレルギー性疾患は増加しつつある．診断および最適な治療選択のためにも，軽度の脊髄炎や末梢神経障害患者ではアトピー素因の有無の問診が重要と考えられる．

文献

1) Kira J, et al: Acute myelitis associated with hyperIgEemia and atopic dermatitis. J Neurol Sci 148(2): 199-203, 1997.
2) Osoegawa M, et al: Myelitis with atopic diathesis: a nationwide survey of 79 cases in Japan. J Neurol Sci 209(1-2): 5-11, 2003.
3) Isobe N, et al: First diagnostic criteria for atopic myelitis with special reference to discrimination from myelitis-onset multiple sclerosis. J Neurol Sci 316(1-2): 30-35, 2012.
4) Isobe N, et al: Neural damage associated with atopic diathesis: a nationwide survey in Japan. Neurology 73(10): 790-797, 2009.
5) Yoon JH, et al: Clinical and laboratory characteristics of atopic myelitis: Korean experience. J Neurol Sci 285(1-2): 154-158, 2009.

6) Gregoire SM, et al: Atopic myelitis: a clinical, biological, radiological and histopathological diagnosis. J Neurol Sci **247**(2): 231-235, 2006.
7) Tanaka M, et al: Distinct CSF cytokine/chemokine profiles in atopic myelitis and other causes of myelitis. Neurology **71**(13): 974-981, 2008.
8) Arima Y, et al: Regional neural activation defines a gateway for autoreactive T cells to cross the blood-brain barrier. Cell **148**(3): 447-457, 2012.
9) Sullivan SK, et al: MIP-3alpha induces human eosinophil migration and activation of the mitogen-activated protein kinases (p42/p44 MAPK). J Leukoc Biol **66**(4): 674-682, 1999.
10) Osoegawa M, et al: Eosinophilic myelitis associated with atopic diathesis: a combined neuroimaging and histopathological study. Acta Neuropathol **105**(3): 289-295, 2003.
11) Murai H, et al: Effect of immunotherapy in myelitis with atopic diathesis. J Neurol Sci **227**(1): 39-47, 2004.

Journal of Neuroimmunology 251 (2012) 110–113

Contents lists available at SciVerse ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

*HLA-DPB1*0201* is associated with susceptibility to atopic myelitis in Japanese

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ARTICLE INFO

Article history:
Received 13 March 2012
Received in revised form 4 June 2012
Accepted 18 July 2012

Keywords:
Atopic myelitis
HLA
Neurogenetics

ABSTRACT

To determine the relationship between susceptibility to atopic myelitis (AM) and polymorphisms of the human leukocyte antigen (*HLA*)-*DPB1* and -*DRB1* alleles, we compared each phenotype frequency between 55 AM patients and 367 unrelated healthy controls in Japan. The *HLA-DPB1*0201* allele was significantly more frequent in AM patients than in healthy controls (54.5% vs. 31.9%, corrected P value = 0.0150, odds ratio = 2.564, 95% confidence interval = 1.444–4.554). Our result suggests that the immunogenetic background of AM differs from that of other CNS autoimmune diseases, such as multiple sclerosis and neuromyelitis optica, which show distinct HLA class II associations.

1. Introduction

A previous histologic study of biopsied spinal cord specimens of atopic myelitis (AM) patients showed eosinophilic inflammation (Osoegawa et al., 2003). In addition, both CCL11/eotaxin, a chemokine for eosinophils, and interleukin (IL)-9, a cytokine secreted by type 2 helper T cells, were markedly up-regulated in the cerebrospinal fluid (CSF) of AM patients, and that disease severity increased with the levels of these molecules (Tanaka et al., 2008). These results indicated that AM might be an autoimmune disease associated with atopic diathesis. Susceptibility to AM is thought to be controlled by the interaction between multiple genetic and environmental factors, as observed in other atopic disorders. The latter encompass common environmental antigens, such as pollens, foods, and house dust mites. However, the genetic background of patients with AM has never been studied.

Human leukocyte antigen (HLA) plays important roles in inducing both autoimmune and atopic diseases. Therefore, polymorphisms in the genes encoding HLA molecules confer susceptibility and resistance to such conditions. We aimed to determine the association between HLA class II genes and the development of AM in the Japanese, focusing on the *HLA-DPB1* and -*DRB1* alleles.

2. Methods

2.1. Patients

In the present study, AM was defined as myelitis of unknown cause with either 1) hyperIgEaemia (>240 U/mL) plus allergen-specific IgE positivity, or 2) coexistent or past atopic diseases, excluding other diseases that may cause myelitis or myelopathy (Tanaka et al., 2008). Atopic diseases included atopic dermatitis, bronchial asthma, allergic rhinitis, and allergic conjunctivitis. The levels of specific IgEs against common allergens, such as *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, pollen, and house dusts, were measured. The existence of myelitis was confirmed by neurological examination, CSF study, magnetic resonance imaging (MRI) of the spinal cord, motor-evoked potentials (MEPs), or somatosensory-evoked potentials (SEPs). Fifty-five consecutive patients, who were diagnosed with AM in the Department of Neurology at Kyushu University Hospital between 1996 and 2011, and whose DNA was available, were enrolled after informed consent was obtained. This study was approved by the Kyushu University Ethics Committee.

The disability status of patients was evaluated on the basis of functional system scores and the expanded disability status scale (Kurtzke, 1983) at disease onset and latest examination. We also used the Multiple Sclerosis Severity Score for evaluation of disability progression, originally assessed in multiple sclerosis (MS) patients (Roxburgh et al., 2005). MRI scans, MEPs, SEPs, and nerve conduction studies were conducted as described previously (Tanaka et al., 2008). The upper normal limits of serum IgE and blood eosinophil counts were set at 240 U/mL and 500/mL, respectively. The CSF levels of IL-9 and CCL11/eotaxin were measured by a fluorescent bead-based immunoassay, and the upper limits were 14.0 pg/mL and 2.2 pg/mL, respectively,

Abbreviations: AM, atopic myelitis; CSF, cerebrospinal fluid; HCs, healthy controls; HLA, human leukocyte antigen; IL, interleukin; MRI, magnetic resonance imaging; MEP, motor evoked potential; MS, multiple sclerosis; SEP, somatosensory evoked potential.

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http://dx.doi.org/10.1016/j.jneuroim.2012.07.007

based on a preliminary study of patients with non-inflammatory neurological disease (Tanaka et al., 2008).

At least one of the following three treatments was administered to 36 patients after obtaining informed consent (Murai et al., 2004). First, corticosteroids were administered by intravenous injection of methylprednisolone at 1,000 mg/day for 3 days followed by oral prednisolone with gradual tapering. Second, intravenous immunoglobulin therapy was administered via drip infusion of gamma globulin at a dose of 400 mg/kg/day for five consecutive days. Third, plasma exchange was performed three times at 2–3-day intervals. Therapeutic efficacies were evaluated based on neurological examination, MRI, MEPs, and SEPs (Murai et al., 2004). Neurological examination was performed before and 2–4 weeks after each treatment, and improvement in any neurological symptom or sign was considered to indicate effectiveness. MRI was performed before and after the treatments, and the effects were evaluated by expert neuroradiologists without knowledge of the treatment modality. MEPs and SEPs were performed as described previously, and on follow-up studies, the evoked potentials were considered improved when unevoked potentials became evoked, or when a delayed peak shifted forward to fall within the normal limits.

2.2. HLA-DPB1 and -DRB1 genotyping

Genomic DNA was extracted from peripheral white blood cells. The *HLA-DRB1* and *-DPB1* alleles were determined by hybridization of the products of PCR amplification of the *HLA-DPB1* or *-DRB1* genes with sequence-specific oligonucleotide probes, as described previously. As controls, 367 unrelated healthy Japanese adults were enrolled.

2.3. Statistical analysis

Differences between the two groups were analyzed by the chi-squared test or Fisher's exact probability test if the numbers were small. Values that were not normally distributed were compared using the Mann–Whitney *U* test. Corrected *P* values were obtained by multiplying uncorrected *P* values by the number of comparisons indicated in the footnote of each table (Bonferroni–Dunn's correction). The threshold for statistical significance was set at $P<0.05$. Odds ratios were calculated according to the method of Woolf. Statistical analyses were conducted using JMP® 8.0 software (SAS Institute, Cary, NC).

3. Results

3.1. HLA-DPB1 and -DRB1 alleles

The phenotype frequencies of the *HLA-DPB1* and *-DRB1* alleles of AM patients and those of healthy controls (HCs) were compared. We observed 15 *DPB1* alleles and 29 *DRB1* alleles (Tables 1, 2). The *DPB1*0201* allele occurred more frequently in AM patients than in HCs, even after correction was made (54.5% vs. 31.9%, uncorrected *P* value = 0.0010, corrected *P* value = 0.0150), and only this allele was associated with a significantly increased risk for AM (odds ratio = 2.564, 95% confidence interval = 1.444–4.554). By contrast, no statistically significant differences in phenotype frequencies were found for the other *DPB1* alleles or any of the *DRB1* alleles between AM patients and HCs. In the present study, protective alleles were not seen in AM patients.

3.2. Comparison of clinical characteristics of AM patients with and without the HLA-DPB1*0201 allele

To investigate the relationship between the *DPB1*0201* allele and the clinical characteristics (of ?), AM patients were stratified according to *DPB1*0201* allele positivity; then, the clinical features were compared between the two groups. There were no significant differences in sex, age of onset, prevalence of atopic diseases, clinical course, disease severity, laboratory findings, MRI findings, electrophysiological findings, or efficacy of treatment between the two groups (Table 3).

Table 1
Phenotype frequencies of *HLA-DPB1* alleles.

*DPB1**	AM patients $n=55$ (%)	HCs $n=367$ (%)	P^{uncorr}	[a] P^{corr}
0201	30 (54.5)	117 (31.9)	0.0010	0.0150
0202	5 (9.1)	19 (5.2)	0.2425	NS
0301	4 (7.3)	16 (4.4)	0.3430	NS
0401	6 (10.9)	46 (12.5)	0.7324	NS
0402	9 (16.4)	64 (17.4)	0.8441	NS
0501	32 (58.2)	240 (65.4)	0.2973	NS
0601	0 (0.0)	6 (1.6)	0.3395	NS
0901	8 (14.5)	80 (21.8)	0.2169	NS
1301	1 (1.8)	19 (5.2)	0.2743	NS
1401	2 (3.6)	10 (2.7)	0.7045	NS
1601	0 (0.0)	2 (0.5)	0.5832	NS
1701	0 (0.0)	2 (0.5)	0.5832	NS
1901	0 (0.0)	3 (1.8)	0.5010	NS
2201	0 (0.0)	1 (0.3)	0.6983	NS
4101	0 (0.0)	1 (0.3)	0.6983	NS

Abbreviations: AM = atopic myelitis; P^{corr} = corrected *P* values; HCs = healthy controls; HLA = human leukocyte antigen; NS = not significant; P^{uncorr} = uncorrected *P* values.
[a] P^{uncorr} was corrected by multiplying the value by 15 to calculate P^{corr}.

4. Discussion

The present study is the first to demonstrate an association between HLA polymorphisms and AM: specifically, the *HLA-DPB1*0201* allele was significantly associated with susceptibility to AM in the Japanese. However, there were no significant differences in clinical features between AM patients carrying or not carrying the *HLA-DPB1*0201* allele.

Table 2
Phenotype frequencies of *HLA-DRB1* alleles.

*DRB1**	AM patients $n=55$ (%)	HCs $n=367$ (%)	P^{uncorr}	[a] P^{corr}
0101	8 (14.5)	51 (13.9)	0.8970	NS
0201	1 (1.8)	0 (0.0)	0.1303	NS
0301	0 (0.0)	2 (0.5)	0.5832	NS
0401	3 (5.5)	4 (1.1)	0.0501	NS
0403	2 (3.6)	18 (4.9)	0.6797	NS
0405	20 (36.4)	98 (26.7)	0.1366	NS
0406	3 (5.5)	23 (6.3)	0.8152	NS
0407	0 (0.0)	2 (0.5)	0.5832	NS
0410	1 (1.8)	4 (1.1)	0.6416	NS
0701	0 (0.0)	2 (0.5)	0.5832	NS
0802	3 (5.5)	26 (7.1)	0.6559	NS
0803	6 (10.9)	58 (15.8)	0.3453	NS
0901	12 (21.8)	101 (27.5)	0.3731	NS
1001	0 (0.0)	4 (1.1)	0.4366	NS
1101	0 (0.0)	16 (4.4)	0.1144	NS
1106	0 (0.0)	1 (0.3)	0.6983	NS
1201	6 (10.9)	33 (9.0)	0.1947	NS
1202	0 (0.0)	13 (3.5)	0.1563	NS
1301	0 (0.0)	1 (0.3)	0.6983	NS
1302	7 (12.7)	49 (13.4)	0.8987	NS
1402	1 (1.8)	0 (0.0)	0.1303	NS
1403	4 (7.3)	8 (2.2)	0.0575	NS
1405	1 (1.8)	14 (3.8)	0.4558	NS
1406	1 (1.8)	8 (2.2)	0.8626	NS
1454	2 (3.6)	19 (5.2)	0.6241	NS
1501	7 (12.7)	60 (16.3)	0.4931	NS
1502	9 (16.4)	80 (21.8)	0.3569	NS
1601	0 (0.0)	1 (0.3)	0.6983	NS
1602	0 (0.0)	3 (0.8)	0.5010	NS

Abbreviations: AM = atopic myelitis; P^{corr} = corrected *P* values; HCs = healthy controls; HLA = human leukocyte antigen; NS = not significant; P^{uncorr} = uncorrected *P* values.
[a] P^{uncorr} was corrected by multiplying the value by 29 to calculate P^{corr}.

Table 3
Demographic features of enrolled AM patients with and without the *HLA-DPB1*0201* allele.

	*DPB1*0201* (+)[a]	*DPB1*0201* (−)[a]	*P* value
Number of patients	30	25	NA
Sex (male/female)	16/14	16/9	0.4246
Age at onset	36.4 ± 13.3	35.1 ± 15.3	0.4751
Disease duration	9.4 ± 5.0	9.8 ± 3.7	0.4919
Atopic diseases	27/30 (90.0)	21/25 (84.0)	0.5062
Atopic dermatitis	9/30 (30.0)	9/25 (36.0)	0.6368
Bronchial asthma	11/30 (36.7)	10/25 (40.0)	0.8000
Allergic rhinitis	15/30 (50.0)	12/25 (48.0)	0.8826
Allergic conjunctivitis	4/30 (13.3)	2/25 (8.0)	0.5276
Other allergies	8/30 (26.7)	6/25 (24.0)	0.8212
Disease onset			
Acute	7/30 (23.3)	9/25 (36.0)	0.3031
Subacute	9/30 (30.0)	6/25 (24.0)	0.6188
Chronic	14/30 (46.7)	10/25 (40.0)	0.6196
Disease course			
Monophasic	7/30 (23.3)	7/25 (28.0)	0.6924
Chronic/fluctuating	18/30 (60.0)	12/25 (48.0)	0.3735
Progressive	5/30 (16.7)	6/25 (24.0)	0.4984
Initial EDSS score	2.0 ± 1.4	2.3 ± 1.6	0.3048
Final FS scores			
Pyramidal	2.1 ± 1.2	2.4 ± 1.7	0.4207
Sensory	2.1 ± 1.3	2.4 ± 1.5	0.3248
Final EDSS score	3.1 ± 1.5	3.6 ± 1.8	0.2362
MSSS	4.29 ± 2.23	4.85 ± 2.47	0.4268
Laboratory findings[b]			
Blood eosinophil count (/mL)	377 ± 453	288 ± 249	0.8525
Serum total IgE (U/mL)	1071 ± 1205	1966 ± 2868	0.4570
IL-9 in CSF (pg/mL)	15.9 ± 4.2	13.0 ± 3.5	0.1967
CCL11/eotaxin in CSF (pg/mL)	4.1 ± 0.8	3.8 ± 0.5	0.3017
OCB (+)	1/28 (3.6)	1/24 (12.5)	0.8053
MRI findings			
Brain lesion	1/20 (5.0)	1/19 (5.3)	0.9703
Cervical cord lesion	8/28 (28.6)	12/23 (52.2)	0.0858
Thoracic cord lesion	6/28 (21.4)	4/23 (17.4)	0.7178
Lumbosacral cord lesion	0/28 (0.0)	0/24 (0.0)	NA
Electrophysiological findings			
MEP central abnormalities	11/30 (36.7)	10/25 (40.0)	0.8000
MEP peripheral abnormalities	3/30 (10.0)	3/25 (12.0)	0.8127
SEP central abnormalities	12/30 (40.0)	5/25 (20.0)	0.1100
SEP peripheral abnormalities	1/30 (3.3)	2/25 (8.0)	0.4479
NCS abnormalities	8/23 (34.8)	4/22 (18.2)	0.2081
Treatment			
mPSL pulse therapy	18/29 (62.1)	15/23 (65.2)	0.8149
Effective	15/18 (83.3)	11/15 (73.3)	0.4841
PE	13/29 (44.8)	9/23 (39.1)	0.6796
Effective	10/13 (76.9)	8/9 (88.9)	0.4743
IVIG	6/29 (20.7)	5/23 (21.7)	0.9267
Effective	1/6 (16.7)	3/5 (60.0)	0.1368

Abbreviations: AM = atopic myelitis; CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale of Kurtzke; FS = functional system; HCs = healthy controls; HLA = human leukocyte antigen; IgE = immunoglobulin E; IgG = immunoglobulin G; IL-9 = interleukin-9; IVIG = intravenous immunoglobulin therapy; MRI = magnetic resonance imaging; MEP = motor evoked potential; mPSL = methylprednisolone; MSSS = Multiple Sclerosis Severity Score; NCS = nerve conduction study; NA = not applicable; OCB = oligoclonal bands; PE = plasma exchange; SEP = somatosensory evoked potential.

[a] Percentages are shown in parentheses.

[b] Upper normal limits: 240 U/mL for serum IgE; 500/mL for blood eosinophil count; 14.0 pg/mL for IL-9 in CSF; 2.2 pg/mL for CCL11/eotaxin in CSF.

Our results indicate that this allele is a genetic risk factor for AM, particularly in Japan, although its presence does not affect the phenotype.

Our study is, inevitably, limited in two ways. First, the numbers of enrolled AM patients were not large owing to the rarity of the disease. Second, this was a single-center study, thus limiting the extrapolation of our results. However, this is the first HLA association study of well-characterized cases to be undertaken. In addition, the association of *HLA-DPB1*0201* with AM remained statistically significant after the appropriate corrections for multiple comparisons were made. We hope this will provide a basis for future studies and that this association will be confirmed in a larger scale study in which we can investigate cohorts from multiple-centers including different geographic areas within Japan, or even internationally.

In Japan, susceptibility to conventional MS is associated with the *HLA-DRB1*1501* allele, as seen in Caucasian patients with MS (Kira et al., 1996). By contrast, neuromyelitis optica and anti-aquaporin 4 antibody-positive opticospinal MS are associated with the *HLA-DPB1*0501* allele (Matsushita et al., 2009). Furthermore, the *HLA-DRB1*0901* allele confers marked resistance to MS in the Japanese (Matsushita et al., 2009) and Chinese (Qiu et al., 2010), while such an association was not found in AM patients. Therefore, AM is considered to have a distinct genetic background from either MS or neuromyelitis optica, suggesting different mechanisms underlying their pathogenesis or the involvement of auto-antigens in AM, despite the fact that all these diseases involve spinal cord lesions.

The *HLA-DPB1*0201* allele has been shown to be associated with chronic beryllium disease (Dai et al., 2010), childhood-onset type 1 diabetes in Japan (Nishimaki et al., 2000), a certain type of rheumatoid arthritis (Carthy et al., 1995), and childhood common acute lymphoblastic leukemia (Taylor et al., 2002). In beryllium disease, an inflammatory $CD4^+$ T cell-mediated lung disease induced by hypersensitivity to beryllium, the way in which *HLA-DP* molecules present beryllium to T cells has been demonstrated by crystal structure analysis of the *HLA-DP* molecule (Dai et al., 2010). Although the molecular mechanisms by which the *HLA-DPB1*0201* allele confers susceptibility to AM remain unclear, environmental allergens, including *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, may bind to an *HLA-DPB1*0201* molecule within a specific peptide-binding groove on dendritic cells, and the resultant complex may induce type 2 T helper cells to secrete soluble mediators, such as IL-4, IL-5, IL-9, IL-13, and CCL11/eotaxin, which drive allergic inflammation. In addition, some cross-reactivity between environmental allergens and CNS antigens may lead to spinal cord inflammation. Additional analysis is required to investigate these possibilities.

Conflict of interest

Dr. Sato reports no disclosures.

Dr. Isobe receives a postdoctoral fellowship from the Uehara Memorial Foundation.

Dr. Yoshimura reports no disclosures.

Dr. Kanamori reports no disclosures.

Dr. Masaki reports no disclosures.

Dr. Matsushita has received speaker honoraria from Bayer Schering Pharma and Pfizer and receives research support from Bayer Schering Pharma, the Ministry of Health, Labour, and Welfare of Japan, the Japan Science and Technology Agency, the Ministry of Education, Culture, Sports, Science, and Technology, Japan, and the Kaibara Morikazu Medical Science Promotion Foundation, Japan.

Dr. Kira serves as an editorial board member of *Multiple Sclerosis*, *The Open Neurology Journal*, and *Journal of the Neurological Sciences*. He is a consultant for Biogen Idec Japan, and has received honoraria from Bayer Healthcare and funding for a trip from Bayer Healthcare and Biogen Idec Japan. He is funded by grants from the Japan Science and Technology Agency and the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Acknowledgments

This work was supported, in part, by a Health and Labour Sciences Research Grant on Intractable Diseases (H22-Nanchi-Ippan-130) (Neuroimmunological Diseases, H23-Nanchi-Ippan-017) from the Ministry of Health, Labour, and Welfare, Japan, and a grant-in-aid (Scientific Research B; No. 22390178, Challenging Exploratory Research; No. 23659459) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References

Carthy, D., MacGregor, A., Awomoi, A., Rigby, A.S., Thomson, W., Donn, R., Silman, A., Ollier, W., 1995. HLA-DPB1*0201 is associated with particular clinical features of rheumatoid arthritis. Rev. Rhum. Engl. Ed. 62, 163–168.

Dai, S., Murphy, G.A., Crawford, F., Mack, D.G., Falta, M.T., Marrack, P., Kappler, J.W., Fontenot, A.P., 2010. Crystal structure of HLA-DP2 and implications for chronic beryllium disease. Proc. Natl. Acad. Sci. U. S. A. 107, 7425–7430.

Kira, J., Kanai, T., Nishimura, Y., Yamasaki, K., Matsushita, S., Kawano, Y., Hasuo, K., Tobimatsu, S., Kobayashi, T., 1996. Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders. Ann. Neurol. 40, 569–574.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452.

Matsushita, T., Matsuoka, T., Isobe, N., Kawano, Y., Minohara, M., Shi, N., Nishimura, Y., Ochi, H., Kira, J., 2009. Association of the HLA-DPB1*0501 allele with anti-aquaporin-4 antibody positivity in Japanese patients with idiopathic central nervous system demyelinating disorders. Tissue Antigens 73, 171–176.

Murai, H., Arahata, H., Osoegawa, M., Ochi, H., Minohara, M., Taniwaki, T., Tobimatsu, S., Mihara, F., Tsuruta, Y., Inaba, S., Kira, J., 2004. Effect of immunotherapy in myelitis with atopic diathesis. J. Neurol. Sci. 227, 39–47.

Nishimaki, K., Kawamura, T., Inada, H., Yagawa, K., Nose, Y., Nabeya, N., Isshiki, G., Tatsumi, N., Niihira, S., 2000. HLA DPB1*0201 gene confers disease susceptibility in Japanese with childhood onset type I diabetes, independent of HLA-DR and DQ genotypes. Diabetes Res. Clin. Pract. 47, 49–55.

Osoegawa, M., Ochi, H., Kikuchi, H., Shirabe, S., Nagashima, T., Tsumoto, T., Tamura, Y., Yamabe, K., Takahashi, H., Iwaki, T., Kira, J., 2003. Eosinophilic myelitis associated with atopic diathesis: a combined neuroimaging and histologic study. Acta Neuropathol. 105, 289–295.

Qiu, W., James, I., Carroll, W.M., Mastaglia, F.L., Kermode, A.G., 2010. HLA-DR allele polymorphism and multiple sclerosis in Chinese populations: a meta-analysis. Mult. Scler. 17, 382–388.

Roxburgh, R.H., Seaman, S.R., Masterman, T., Hensiek, A.E., Sawcer, S.J., Vukusic, S., Achiti, I., Confavreux, C., Coustans, M., le Page, E., Edan, G., McDonnell, G.V., Hawkins, S., Trojano, M., Liguori, M., Cocco, E., Marrosu, M.G., Tesser, F., Leone, M.A., Weber, A., Zipp, F., Miterski, B., Epplen, J.T., Oturai, A., Sørensen, P.S., Celius, E.G., Lara, N.T., Montalban, X., Villoslada, P., Silva, A.M., Marta, M., Leite, I., Dubois, B., Rubio, J., Butzkueven, H., Kilpatrick, T., Mycko, M.P., Selmaj, K.W., Rio, M.E., Sá, M., Salemi, G., Savettieri, G., Hillert, J., Compston, D.A., 2005. Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. Neurology 64, 1144–1151.

Tanaka, M., Matsushita, T., Tateishi, T., Ochi, H., Kawano, Y., Mei, F.J., Minohara, M., Murai, H., Kira, J.I., 2008. Distinct CSF cytokine/chemokine profiles in atopic myelitis and other causes of myelitis. Neurology 71, 974–981.

Taylor, G.M., Dearden, S., Ravetto, P., Ayres, M., Watson, P., Hussain, A., Greaves, M., Alexander, F., Eden, O.B., UKCCS Investigators, United Kingdom Childhood Cancer Study, 2002. Genetic susceptibility to childhood common acute lymphoblastic leukaemia is associated with polymorphic peptide-binding pocket profiles in HLA-DPB1*0201. Hum. Mol. Genet. 11, 1585–1597.

Journal of Neuroimmunology 246 (2012) 108–112

Contents lists available at SciVerse ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Clinical disability progression and platelet GP IIb/IIIa values in patients with atopic myelitis

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ARTICLE INFO

Article history:
Received 2 December 2011
Received in revised form 27 February 2012
Accepted 14 March 2012

Keywords:
Myelitis
Atopy
Progression
Platelet
GP IIb/IIIa
Aggregation

ABSTRACT

We aimed to clarify the disability progression and platelet aggregative function in atopic myelitis (AM). Seventeen AM patients and 35 healthy controls were subjected to clinico-allergological evaluations and glycoprotein IIb/IIIa (GP IIb/IIIa) measurements using a VerifyNow assay system. In AM patients, the disease duration had significant positive correlations with the Kurtzke Expanded Disability Status Scale scores and Sensory Functional Scale scores. The GP IIb/IIIa values were significantly higher in AM patients than in controls as well as in females compared with males. AM is essentially a progressive disease affecting the sensory system, and involves an increased platelet aggregative function.

1. Introduction

We first reported the emergence of myelitis in patients with atopic disorders, and named it atopic myelitis (AM) (Kira et al., 1997, 1998, 1999, 2001). Repeated nationwide surveys of this condition have revealed a widespread occurrence of AM in Japan (Osoegawa et al., 2003a; Isobe et al., 2009). Similar cases have recently been reported in Europe (Zoli et al., 2005; Constantinescu et al., 2006), including a biopsy-proven case showing marked eosinophil infiltration (Gregoire et al., 2006), as well as in East Asia, including a relatively large series from Korea (Yoon et al., 2009). In AM patients, we found that CCL2, a chemokine for eosinophils, and interleukin-9, a T helper 9 cytokine, were both markedly upregulated in the cerebrospinal fluid, and that the levels of these molecules showed strong positive correlations with the disease severity (Tanaka et al., 2008), collectively suggesting that atopy-related inflammation is operative. A histological study of biopsied spinal cord specimens revealed eosinophilic inflammation and simultaneous loss of both axons and myelin (Kikuchi et al., 2001; Osoegawa et al., 2003b). The condition showed a poor response to corticosteroids but responded to plasma exchanges (Murai et al., 2004). However, the disability progression over the clinical course is still ill-defined.

A recent nationwide survey investigating both AM and atopy-related peripheral neuritis (APN), such as Churg–Strauss syndrome (CSS), revealed a considerable overlap between AM and APN (Isobe et al., 2009). In CSS, ischemia of peripheral nerves caused by inflammation is supposed to be the dominant mechanism for neural damage, and even the optic nerve is affected by the ischemic process in this condition (Liou et al., 1994; Giorgi et al., 1997). Atopic disorders have been reported to be associated with cardiovascular diseases (Brunekreef et al., 2000), and platelet activation in allergy is assumed to play a significant role in these situations (Masini et al., 1994). Platelet aggregation is mediated by interactions of fibrinogen with glycoprotein receptors on platelets, such as glycoprotein IIb/IIIa (GP IIb/IIIa) (αIIbβ3 integrin), which is the central receptor for platelet aggregation (Kasperska-Zajac and Rogala, 2007; Pitchford, 2007). Therefore, in the present study, we aimed first to clarify the relationship between the disease duration and disability progression in AM, and second to reveal any platelet aggregative function abnormalities by measuring the GP IIb/IIIa contents.

2. Subjects and methods

2.1. Subjects and clinico-allergological evaluation

AM was defined as myelitis of unknown cause with either (1) hyperIgEemia (>240 U/ml) and antigen-specific IgE positivity or (2) coexistent or past atopic diseases following the diagnostic criteria,

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doi:10.1016/j.jneuroim.2012.03.009

excluding other diseases (Osoegawa et al., 2003a). Bronchial asthma, atopic dermatitis, allergic rhinitis, food allergy and allergic conjunctivitis were regarded as atopic diseases in the present study. The existence of myelitis was confirmed by spinal cord MRI, motor-evoked potentials, somatosensory-evoked potentials or neurological findings of either exaggerated deep tendon reflexes or sensory levels. Detailed clinical information on individual patients, including symptomatology, disability scores including the Kurtzke Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983), Pyramidal Functional Scale (FS) score (Kurtzke, 1983) and Sensory FS score (Kurtzke, 1983), Progression Index (Sanders et al., 1986; Chapman et al., 2001), and allergological, neuroimaging and electrophysiological data, were retrospectively evaluated. All 17 AM patients who visited the Department of Neurology, Kyushu University Hospital, from 1 March 2010 to 31 May 2011 were enrolled in the present study, with no medications within 1 week prior to measurement. The AM patients comprised 6 males and 11 females, with a mean (±SD) age at examination of 43.4±13.2 years, mean age at onset of 36.3±12.2 years and disease duration of 7.0±5.0 years. In addition, 35 healthy controls with no medication were evaluated in this study. The control subjects comprised 16 males and 19 females, with a mean age at examination of 31.6±4.8 years. The sex ratios did not differ significantly between the two groups, while the age at examination was significantly higher in the AM patients than in the controls ($p<0.01$). All the AM patients and controls were subjected to a questionnaire survey for past and present history of the above-mentioned atopic diseases, and underwent routine laboratory tests including blood cell counts (white blood cells, platelets, eosinophils, neutrophils and lymphocytes), hemoglobin, total IgE and common allergen-specific IgE for *Dermatophagoides pteronyssinus* (*Dp*) and *Dermatophagoides farinae* (*Df*). *Dp* was measured in all 17 AM patients, while *Df* was examined in 16 AM patients. This study was approved by the ethical committee of Kyushu University Hospital. Written informed consent was obtained from all subjects.

2.2. Measurement of GP IIb/IIIa

GP IIb/IIIa was assayed as an index of platelet aggregative function using a VerifyNow GP IIb/IIIa assay system (Accumetrics, San Diego, CA; Van Werkum et al., 2008). This spectrophotometric assay system is comparable to other well-established methods for platelet aggregation and produces rapid results with small amounts of whole blood (Matzdorff et al., 2001; Wheeler et al., 2002; White et al., 2004). Fresh venous blood was drawn from the patients and healthy controls, who had received no medications affecting platelet aggregation at least for 1 week prior to the blood drawing, and immediately subjected to the assay according to the manufacturer's recommendations (Accumetrics; Michelson, 2009). The results were expressed as platelet aggregation units (PAU).

2.3. Statistical analysis

First, we examined whether all of the clinical and laboratory data showed normal distributions. Student's *t*-test and Welch's test were used to evaluate the significance of differences between the laboratory and demographic features between the AM patients and controls. When comparing the frequencies of atopic disorders between the AM patients and controls, Fisher's exact probability test was used. Since the GP IIb/IIIa values showed a normal distribution in the subjects, a two-way ANOVA was used to compare the GP IIb/IIIa values by sex and disease. Pearson's r correlation test was used to measure the degrees of the relationships between the GP IIb/IIIa values and clinical and laboratory parameters. The level of statistical significance was set at $p<0.05$. All analyses were performed using SPSS software (SPSS Inc., Chicago, IL).

3. Results

3.1. Demographic features of the AM patients

The AM patients showed EDSS scores of 3.2±1.8 (mean±SD), Pyramidal FS scores of 2.2±1.3, Sensory FS scores of 1.9±1.5 and Progression Indexes of 1.3±1.7. The disease duration showed significant positive correlations with the EDSS scores ($r=0.61$, $p<0.01$) and Sensory FS scores ($r=0.64$, $p<0.01$), but not the Pyramidal FS scores (Fig. 1A, B). There were no sex differences in any of the clinical parameters (data not shown).

3.2. Comparisons of hematological and allergological findings between the AM patients and healthy controls

Compared with the controls, the AM patients had significantly higher frequencies of bronchial asthma ($p<0.001$), allergic rhinitis ($p<0.05$), food allergy ($p<0.05$) and allergic conjunctivitis ($p<0.05$) (Table 1). The IgE levels and neutrophil counts were significantly higher in the AM patients than in the controls ($p<0.05$ for both). The allergen-specific IgE levels did not differ significantly between the AM patients and controls in the present study, including those against *Dp* and *Df*, which probably reflects the small sample size. There were no other significant differences in the routine hematological tests between the two groups. The hemoglobin levels were

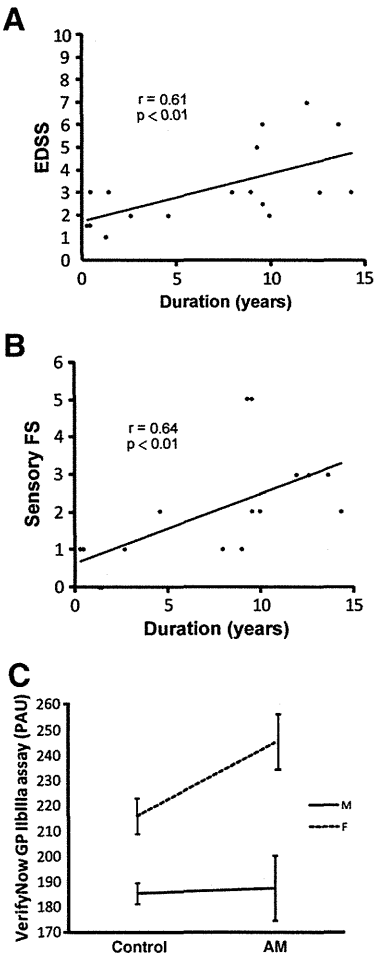

Fig. 1. (A) Correlation between the disease duration and the EDSS scores in the AM patients. (B) Correlation between the disease duration and the Sensory FS scores in the AM patients. (C) Two-way ANOVA of the GP IIb/IIIa values by sex and disease. The GP IIb/IIIa levels are significantly higher in females than in males and in the AM patients compared with the controls. AM: atopic myelitis; EDSS: Expanded Disability Status Scale of Kurtzke's score; FS: Functional Scale; GP IIb/IIIa: glycoprotein IIb/IIIa.

Table 1
Comparisons of the hematological and allergological findings between the AM patients and healthy controls.

	AM patients ($n=17$)	Healthy controls ($n=35$)	p value[a]
Bronchial asthma	7 (41.2%)	1 (2.9%)	<0.001
Atopic dermatitis	5 (29.4%)	5 (14.3%)	NS
Allergic rhinitis	10 (58.8%)	8 (22.9%)	<0.05
Food allergy	6 (35.3%)	3 (8.6%)	<0.05
Allergic conjunctivitis	5 (29.4%)	2 (5.7%)	<0.05
White blood cells (/μl)	7174.7 ± 2212.1	6122.9 ± 967.7	NS
Neutrophils (/μl)	4570.7 ± 1881.7	3417.5 ± 819.4	<0.05
Lymphocytes (/μl)	2010.2 ± 747.1	2088.3 ± 358.4	NS
Eosinophils (/μl)	235.0 ± 173.6	156.7 ± 129.8	NS
Platelets (×10,000/μl)	24.8 ± 5.3	23.3 ± 6.4	NS
Hemoglobin (g/dl)	13.0 ± 1.5	13.9 ± 1.5	NS
Total IgE (IU/ml)	996.5 ± 1619.2	143.2 ± 188.0	<0.05
Allergen specific IgE to *Dermatophagoides pteronyssinus* (UA/ml)	24.6 ± 37.0	9.4 ± 15.4	NS
Allergen specific IgE to *Dermatophagoides farinae* (UA/ml)	23.6 ± 34.6	8.1 ± 13.3	NS

Data are shown as means ± SD.
AM: atopic myelitis; NS: not significant.

significantly higher in males than in females (14.9 ± 1.1 vs. 12.7 ± 1.1 g/dl, $p<0.01$ for all subjects).

3.3. GP IIb/IIIa values and their relationships with clinical parameters

The GP IIb/IIIa values tended to be higher in the AM patients (mean ± SD: 224.8 ± 44.1) than in the healthy controls (201.9 ± 29.5) as a whole group ($p=0.06$). Considering the sex differences as a secondary factor affecting the GP IIb/IIIa differences between the two groups, we performed a two-way ANOVA for further analysis (Fig. 1 C). The two-way ANOVA of the GP IIb/IIIa values by sex and disease revealed significant main effects for sex ($F[1,51]=22.56$, $p<0.01$) and disease ($F[1,51]=4.69$, $p<0.05$). There was no sex-by-disease interaction. Thus, the GP IIb/IIIa values were significantly higher in females than in males in both the AM patients and controls, and were also significantly greater in the AM patients than in the controls.

3.4. Correlations between the GP IIb/IIIa values and clinical parameters

In the AM patients, the GP IIb/IIIa values showed a significant positive correlation with the platelet counts ($r=0.57$, $p<0.05$) (Fig. 2A). In contrast, there was no correlation between the GP IIb/IIIa values and the platelet counts in the controls (Fig. 2A). In the AM patients, there was a significant positive correlation between the platelet counts and eosinophil counts ($r=0.49$, $p<0.05$). In contrast, the platelet counts in the controls had a negative correlation with the eosinophil counts ($r=-0.52$, $p<0.01$) (Fig. 2B). In addition, the platelet counts showed significant positive correlations with both the *Dp* ($r=0.58$, $p<0.05$) and *Df* ($r=0.61$, $p<0.05$) levels (Fig. 2 C). Meanwhile, the GP IIb/IIIa values had a tendency to show a mild negative correlation with the hemoglobin concentrations ($r=-0.48$, $p=0.05$) in the AM patients, while there was a significant negative correlation between the GP IIb/IIIa values and the hemoglobin concentrations in the controls ($r=-0.64$, $p<0.01$) (Fig. 2D). No correlations of the GP IIb/IIIa values were found with the other clinical and laboratory parameters, including age at onset, age at examination, EDSS scores, Pyramidal FS scores, Sensory FS scores, disease duration, Progression Indexes, white blood cell counts, eosinophil counts, neutrophil counts, and total and allergen-specific IgE levels.

4. Discussion

The main new findings of the present study are as follows: (1) in AM patients, the disease duration had significant positive correlations with the EDSS scores and Sensory FS scores, but not the Pyramidal FS scores; (2) the GP IIb/IIIa values were significantly higher in the AM patients than in the controls, as well as in females compared with males; (3) the GP IIb/IIIa levels showed a significant positive correlation with the platelet counts in the AM patients, but not in the controls; and (4) the platelet counts in the AM patients showed significant positive correlations with the eosinophil counts and mite antigen-specific IgE levels.

AM patients predominantly present a fluctuating course of paresthesia/dysesthesia in the distal parts of all four limbs (Osoegawa et al., 2003a; Isobe et al., 2009). The present study has revealed for the first time a positive correlation of the disease duration with the EDSS scores in AM patients, suggesting that AM is essentially a progressive disease in most patients, although superimposed fluctuations of the symptoms may occur (Osoegawa et al., 2003a; Isobe et al., 2009). The disease preferentially affects the posterior column of the spinal cord radiologically as well as pathologically, which is in accord with the positive correlation of the disease duration with the Sensory FS scores but not the Pyramidal FS scores. Thus, the disability of AM patients over the clinical course is considered to be determined by the posterior column sensory impairment.

The GP IIb/IIIa values had a significant negative correlation with the hemoglobin levels in the controls and showed a tendency toward a negative correlation with the hemoglobin levels in the AM patients. This may be explained by the methodological reason that the VerifyNow system is a kind of turbidity assay, which leads us to a cautious interpretation of the results. The lower GP IIb/IIIa levels in males compared with females may partly reflect the higher hemoglobin levels in males than in females, because higher hemoglobin amounts reduce the absorbance, thereby lowering the GP IIb/IIIa levels in the present assay. However, Faraday et al. (1997) reported that a higher proportion of GP IIb/IIIa was activated in females compared with males, suggesting that the elevated GP IIb/IIIa levels in females may represent a physiological sex difference in platelet activity. In the present study, however, the hemoglobin levels did not differ significantly between the AM patients and controls. Furthermore, although the age at examination was higher in the AM patients than in the controls, the GP IIb/IIIa values had no correlation with the age at examination. Thus, the elevated GP IIb/IIIa levels in the AM patients are supposed to be real rather than artifacts.

Activated GP IIb/IIIa binds to fibrinogen or von Willebrand factor, thereby forming molecular bridges between aggregating platelets, and an increased amount of GP IIb/IIIa is associated with a higher platelet aggregation function (Yakushkin et al., 2011). Therefore, the increased GP IIb/IIIa amounts in the AM patients suggest a possible exaggerated reactivity of platelets in this condition *in vivo*. Atopy-related neural disorders, in which microcirculatory disturbance is

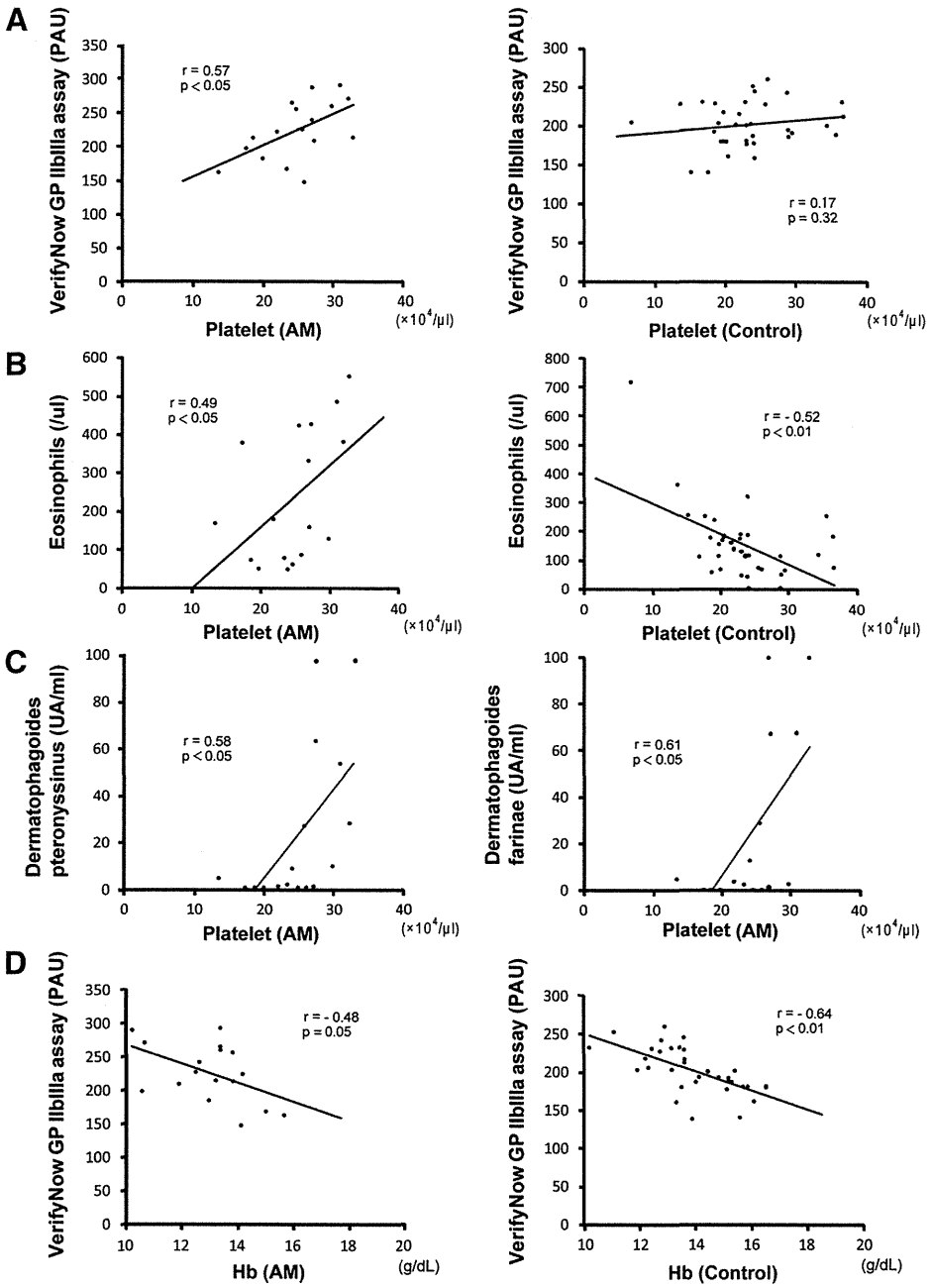

Fig. 2. (A) Correlation between the GP IIb/IIIa values and the platelet counts in the AM patients and controls. (B) Correlation between the eosinophil counts and the platelet counts in the AM patients and controls. (C) Correlation between the *Dp*- and *Df*-specific IgE levels and the platelet counts. (D) Correlation between the GP IIb/IIIa values and the hemoglobin concentrations in the AM patients and controls. GP IIb/IIIa: glycoprotein IIb/IIIa; AM: atopic myelitis; *Df*: *Dermatophagoides farinae*; *Dp*: *Dermatophagoides pteronyssinus*.

assumed, are not only limited to CSS, but may also exist in several other neurological conditions associated with atopic diathesis, such as juvenile muscular atrophy of the distal upper limb (Hiramaya disease) (Hirayama et al., 1959) and Hopkins syndrome (Hopkins, 1974). We (Kira and Ochi, 2001) and others (Ito et al., 2005) reported an association of atopic diathesis with Hirayama disease, in which shrinkage and necrosis of the anterior horns of the cervical spinal cord were noted at autopsy (Hirayama et al., 1987). Another rare disease is an acute poliomyelitis-like illness known as Hopkins syndrome (asthmatic amyotrophy). The disease presents as sudden onset of flaccid paralysis following asthma attacks in children (Ito et al., 2005), and responds poorly to corticosteroids in most cases (Shahar et al., 1991). We also reported cases of AM showing focal amyotrophy and anterior horn cell involvement (Tokunaga et al., 2004; Kira et al., 2008), suggesting possible links of AM with Hopkins syndrome and Hirayama disease (Kira et al., 2008). In Hirayama disease, repeated microcirculatory disturbances are assumed to cause anterior horn cell necrosis, which is vulnerable to ischemia (Hirayama, 2000).

It has been shown that intravascular platelet activation is necessary for the development of chronic airway inflammation (Kowal et al., 2006; Pitchford and Page, 2006). In the acute phase of asthma attacks, not only eosinophils but also platelet activation markers, such as β-thromboglobulin, platelet factor-4 and soluble P-selectin, are elevated during allergen challenge with *Dp* (Kowal et al., 2006). It was reported that eosinophils from allergic patients showed enhanced interactions with platelets, and that P-selection on platelets bound to eosinophils reinforced the tethering of these cells to endothelia, thereby potentiating the migration of eosinophils into the parenchyma (Ulfman et al., 2003). The significant positive correlations

of the platelet counts with the eosinophil counts and *Dp*- and *Df*-specific IgE levels in AM patients may suggest a possible positive interaction of these factors. It is possible that elevated mite antigen-specific IgE may potentiate the migration of increased numbers of eosinophils into the inflamed spinal cord through eosinophil/platelet interactions, thereby contributing to the tissue damage in AM patients.

In the present study, we have revealed that AM is a progressive disease and that the platelet aggregative function is increased in AM. Thus, long-term use of an anti-platelet agent may be worth trying to prevent disease progression in this condition.

Acknowledgment

This work was supported in part by a Health and Labour Sciences Research Grant on Intractable Diseases (H22-Nanchi-Ippan-130) from the Ministry of Health, Labour and Welfare, Japan.

References

Brunekreef, B., Hoek, G., Fischer, P., Spieksma, F.T., 2000. Relation between airborne pollen concentrations and daily cardiovascular and respiratory-disease mortality. Lancet 355, 1517–1518.

Chapman, J., Vinokurov, S., Achiron, A., Karussis, D.M., Mitosek-Szewczyk, K., Birnbaum, M., Michaelson, D.M., Korczyn, A.D., 2001. *APOE* genotype is a major predictor of long-term progression of disability in MS. Neurology 56, 312–316.

Constantinescu, C.S., Thomas, M., Zaman, A.G., 2006. Atopic optic neuritis. Ocul. Immunol. Inflamm. 14, 125–127.

Faraday, N., Goldschmidt-Clermont, P.J., Bray, P., 1997. Gender differences in platelet GP IIb/IIIa activation. Thromb. Haemost. 77, 748–754.

Giorgi, D., Laganà, B., Giorgi, A., Verrasto, G., Grandinetti, F., Grandinetti, P.P., Gabrieli, C.B., 1997. Ischemic optic neuritis in Churg–Strauss syndrome. Recenti. Prog. Med. 88, 273–275.

Gregoire, S.M., Mormont, E., Laloux, P., Godfraind, C., Gilliard, C., 2006. Atopic myelitis: a clinical, biological, radiological and histopathological diagnosis. J. Neurol. Sci. 247, 231–235.

Hirayama, K., 2000. Juvenile muscular atrophy of distal upper extremity. Intern. Med. 39, 283–290.

Hirayama, K., Toyokura, Y., Tsubaki, T., 1959. Juvenile muscular atrophy of unilateral upper extremity: a new clinical entity. Psychiatr. Neurol. Jpn. 61, 2190–2198.

Hirayama, K., Tomonaga, M., Kitano, K., Yamada, T., Kojima, S., Arai, K., 1987. Focal cervical poliopahy causing juvenile muscular atrophy of distal upper extremity: a pathological study. J. Neurol. Neurosurg. Psychiatry 50, 285–290.

Hopkins, I.J., 1974. A new syndrome: poliomyelitis-like illness associated with acute asthma in childhood. Aust. Paediatr. J. 10, 273–276.

Isobe, N., Kira, J., Kawamura, N., Ishizu, T., Arimura, K., Kawano, Y., 2009. Neural damage associated with atopic diathesis. A nationwide surveys in Japan. Neurology 73, 790–797.

Ito, S., Kuwabara, S., Fukutake, T., Tokumaru, Y., Hattori, T., 2005. HyperIgEaemia in patients with juvenile muscular atrophy of the distal upper extremity (Hirayama disease). J. Neurol. Neurosurg. Psychiatry 76, 132–134.

Kasperska-Zajac, A., Rogala, B., 2007. Platelet activation during allergic inflammation. Inflammation 30, 161–166.

Kikuchi, H., Osoegawa, M., Ochi, H., Murai, H., Horiuchi, T., Takahashi, H., Yamabe, K., Iwaki, T., Mizutani, T., Oda, M., Kira, J., 2001. Spinal cord lesions of myelitis with hyperIgEemia and mite antigen specific IgE (atopic myelitis) manifest eosinophilic inflammation. J. Neurol. Sci. 183, 73–78.

Kira, J., Ochi, H., 2001. Juvenile muscular atrophy of the distal upper limb (Hirayama disease) associated with atopy. J. Neurol. Neurosurg. Psychiatry 70, 798–801.

Kira, J., Yamasaki, K., Kawano, Y., Kobayashi, T., 1997. Acute myelitis associated with hyperIgEemia and atopic dermatitis. J. Neurol. Sci. 148, 199–203.

Kira, J., Kawano, Y., Yamasaki, K., Tobimatsu, S., 1998. Acute myelitis with hyperIgEaemia and mite antigen specific IgE: atopic myelitis. J. Neurol. Neurosurg. Psychiatry 64, 676–679.

Kira, J., Kawano, Y., Horiuchi, I., Yamada, T., Imayama, S., Furue, M., Yamasaki, K., 1999. Clinical, immunological and MRI features of myelitis with atopic dermatitis (atopic myelitis). J. Neurol. Sci. 162, 56–61.

Kira, J., Horiuchi, I., Suzuki, J., Osoegawa, M., Tobimatsu, S., Murai, H., Minohara, M., Furue, M., Ochi, H., 2001. Myelitis associated with atopic disorders in Japan: a retrospective clinical study of the past 20 years. Intern. Med. 40, 613–619.

Kira, J., Isobe, N., Kawano, Y., Osoegawa, M., Ohyagi, Y., Mihara, F., Murai, H., 2008. Atopic myelitis with focal amyotrophy: a possible link to Hopkins syndrome. J. Neurol. Sci. 269, 143–151.

Kowal, K., Pampuch, A., Kowal-Bielecka, O., DuBuske, L.M., Bodzenta-Lukaszyk, A., 2006. Platelet activation in allergic asthma patients during allergen challenge with *Dermatophagoides pteronyssinus*. Clin. Exp. Allergy 36, 426–432.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452.

Liou, H.H., Yip, P.K., Chang, Y.C., Liu, H.M., 1994. Allergic granulomatosis and angiitis (Churg–Strauss syndrome) presenting as prominent neurologic lesions and optic neuritis. J. Rheumatol. 21, 2380–2384.

Masini, E., Di Bello, M.G., Raspanti, S., Sacchi, T.B., Maggi, E., Mannaioni, P.F., 1994. Platelet aggregation and histamine release by immunological stimuli. Immunopharmacology 28, 19–29.

Matzdorff, A.C., Kühnel, G., Kemkes-Matthes, B., Voss, R., 2001. Comparison of GP IIB/IIIA inhibitors and their activity as measured by aggregometry, flow cytometry, single platelet counting, and the rapid platelet function analyzer. J. Thromb. Thrombolysis 12, 129–139.

Michelson, A.D., 2009. Methods of the measurement of Platelet Function. Am. J. Cardiol. 103, 20A–26A.

Murai, H., Arahata, H., Osoegawa, M., Ochi, H., Minohara, M., Taniwaki, T., Tobimatsu, S., Mihara, F., Tsuruta, Y., Inaba, S., Kira, J., 2004. Effect of immunotherapy in myelitis with atopic diathesis. J. Neurol. Sci. 227, 39–47.

Osoegawa, M., Ochi, H., Minohara, M., Murai, H., Umehara, F., Furuya, H., Yamada, T., Kira, J., 2003a. Myelitis with atopic diathesis: a nationwide survey of 79 cases in Japan. J. Neurol. Sci. 209, 5–11.

Osoegawa, M., Ochi, H., Kikuchi, H., Shirabe, S., Nagashima, T., Tsumoto, T., Tamura, Y., Yamabe, K., Takahashi, H., Iwaki, T., Kira, J., 2003b. Eosinophilic myelitis associated with atopic diathesis: a combined neuroimaging and histopathological study. Acta Neuropathol. 105, 289–295.

Pitchford, S.C., 2007. Novel uses for anti-platelet agents as anti-inflammatory drugs. Br. J. Pharmacol. 152, 987–1002.

Pitchford, S.C., Page, C.P., 2006. Platelet activation in asthma: integral to the inflammatory response. Clin. Exp. Allergy 36, 399–401.

Sanders, E.A., Bollen, E.L., van der Velde, E.A., 1986. Presenting signs and symptoms in multiple sclerosis. Acta Neurol. Scand. 73, 269–272.

Shahar, E.M., Hwang, P.A., Niesen, C.E., Murphy, E.G., 1991. Poliomyelitis-like paralysis during recovery from acute bronchial asthma: possible etiology and risk factors. Pediatrics 88, 276–279.

Tanaka, M., Matsushita, T., Tateishi, T., Ochi, H., Kawano, Y., Mei, F.-J., Minohara, M., Murai, H., Kira, J., 2008. Distinct CSF cytokine/chemokine profiles in atopic myelitis and other causes of myelitis. Neurology 71, 974–981.

Tokunaga, H., Osoegawa, M., Murai, H., Ochi, H., Minohohara, M., Taniwaki, T., Kira, J., 2004. Anterior horn cell involvement in myelitis with atopic diathesis (atopic myelitis). Fukuoka Igaku Zasshi 95, 36–43.

Ulfman, L.H., Joosten, D.P.H., van Aalst, C.W., Lammers, J.-W.J., van de Graaf, E.A., Koenderman, L., Zwaginga, J.J., 2003. Platelets promote eosinophil adhesion of patients with asthma to endothelium under flow conditions. Am. J. Respir. Cell Mol. Biol. 28, 512–519.

Van Werkum, J.W., Harmsze, A.M., Elsenberg, E.H., Bouman, H.J., Ten Berg, J.M., Hackeng, C.M., 2008. The use of the VerifyNow system to monitor antiplatelet therapy: a review of the current evidence. Platelets 19, 479–488.

Wheeler, G.L., Braden, G.A., Steinhubl, S.R., Kereiakes, D.J., Kottke-Marchant, K., Michelson, A.D., Furman, M.I., Mueller, M.N., Moliterno, D.J., Sane, S.C., 2002. The Ultegra rapid platelet-function assay: comparison to standard platelet function assays in patients undergoing percutaneous coronary intervention with abciximab therapy. Am. Heart J. 143, 602–611.

White, M.M., Krishnan, R., Kueter, T.J., Jacoski, M.V., Jennings, L.K., 2004. The use of the point of care Helena ICHOR/Plateletworks and the Accumetrics Ultegra RPFA for assessment of platelet function with GPIIb-IIIa antagonists. J. Thromb. Thrombolysis 18, 163–169.

Yakushkin, V.V., Zyuryaev, I.T., Khaspekova, S.G., Sirotkina, O.V., Ruda, M.Y., Mazurov, A.V., 2011. Glycoprotein IIb-IIIa content and platelet aggregation in healthy volunteers and patients with acute coronary syndrome. Platelets 22, 243–251.

Yoon, J.H., Joo, I.S., Li, W.Y., Sohn, S.Y., 2009. Clinical and laboratory characteristics of atopic myelitis: Korean experience. J. Neurol. Sci. 285, 154–158.

Zoli, A., Mariano, M., Fusari, A., Bonifazi, F., Antonicelli, L., 2005. Atopic myelitis: first case report outside Japan? Allergy 60, 410–411.

Journal of the Neurological Sciences 316 (2012) 30–35

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

First diagnostic criteria for atopic myelitis with special reference to discrimination from myelitis-onset multiple sclerosis

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ARTICLE INFO

Article history:
Received 5 July 2011
Received in revised form 15 January 2012
Accepted 2 February 2012
Available online 25 February 2012

Keywords:
Atopic myelitis
Diagnostic criteria
Multiple sclerosis
Allergen-specific IgE
IL9
CCL11/eotaxin

ABSTRACT

Objective: To establish the first evidence-based diagnostic criteria for atopic myelitis (AM) enabling it to be discriminated from myelitis-onset multiple sclerosis (MS), which is a difficult differential diagnosis.
Methods: Sixty-nine consecutive AM patients examined from 1996 to 2010 at Kyushu University hospital, who fulfilled the empirical definition of AM (2003), and 51 myelitis-onset MS patients in whom allergen-specific IgE was measured, were enrolled. The first available brain MRI findings were compared between the two. Then, we compared the clinical and laboratory features between the 16 AM cases who did not meet the Barkhof brain MRI criteria for MS after more than 5 years follow-up and 51 myelitis-onset MS cases. Based on the discriminative findings, we established diagnostic criteria for AM and calculated the sensitivity and specificity.
Results: AM patients had a significantly lower frequency of Barkhof brain lesions on baseline MRI than myelitis-onset MS patients. AM patients had a significantly higher frequency of present and/or past history of atopic disease and hyperIgEemia, and higher cerebrospinal fluid levels of interleukin 9 and CCL11/eotaxin, but a lower frequency of oligoclonal IgG bands than myelitis-onset MS patients. Our proposed diagnostic criteria for AM demonstrated 93.3% sensitivity and 93.3% specificity for AM against myelitis-onset MS, with 82.4% positive predictive value and 97.7% negative predictive value.
Conclusion: Our first evidence-based criteria for AM show high sensitivity and specificity, and would be useful clinically.

1. Introduction

Atopic myelitis (AM) is related to atopic diathesis, mainly atopic disorders such as atopic dermatitis, atopic rhinitis, and bronchial asthma [1]. Since we reported the first cases in 1996 [1], similar clinical and even pathologically confirmed cases [2,3] have been reported from other facilities, mainly in Japan with some from Korea and European countries, and its demographic features have gradually been clarified. Repeated nationwide surveys of AM in Japan have revealed that patients with AM most commonly show cervical cord involvement, mainly in the posterior column, preferentially demonstrating sensory impairment in the four limbs, while motor weakness and muscle atrophy were more frequently seen in those with bronchial asthma than in those with other atopic disorders [4,5]. Such features were similar to those reported in 14 AM patients from Korea [6], although a few differences were noted, such as lower prevalence of a history of atopic diseases, thoracic cord preference, and higher frequencies of gadolinium-enhanced lesions compared with nationwide surveys in Japan. In addition, the nationwide surveys investigating AM and atopy-related peripheral neuritis, such as Churg–Strauss syndrome, have revealed that the clinical or laboratory data from approximately a quarter of AM patients indicated the simultaneous involvement of the peripheral nerves, which thus suggests an overlap with Churg–Strauss syndrome [5]. Moreover, we recently reported the distinct immunological features of AM by cytokine assays of cerebrospinal fluid (CSF): CCL11/eotaxin and interleukin 9 (IL9) were specifically increased in AM patients, but not in patients with other causes of myelitis, including multiple sclerosis (MS), Sjögren syndrome, and HTLV-1-associated myelopathy [7]. Moreover, the increase in IL9 and CCL11/eotaxin showed a significant correlation with disease severity [7]. Collectively, these findings suggest that AM has a mechanism fundamentally distinct from that of MS.

We used the empirical definitions of AM in the first and second nationwide surveys in Japan [4,5]; the first survey defined AM as myelitis of unknown cause with either (1) hyperIgEemia plus mite

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doi:10.1016/j.jns.2012.02.007