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Ⅱ. 研究成果解説資料

免疫性神経疾患に関する調査研究班 (平成 14 年度～平成 16 年度)
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多発性硬化症全国臨床疫学調査2004年 —15年ぶりのMS全国調査を実施—

1次調査結果

	対象数	発送数	抽出率	回答数	回答率	患者報告数
総数	23338	6708	28.7	3749	55.9	3978
◇内科・神経内科	7340	1993	26.3	966	50.0	2967
◇小児科	3296	945	28.7	651	68.9	75
◇整形外科	5753	1227	21.3	677	55.2	153
◇脳外科	2213	759	34.3	424	55.9	47
◇眼科	2317	831	35.9	471	56.7	496
◇精神科神経科	2403	997	41.5	552	55.4	235
◇その他	16	16	100.0	8	50.0	5

(抽出率、回答率の単位は%、それ以外は人)



「難病の患者数と臨床疫学像把握のための
全国疫学調査マニュアル」に基づき

男3000人(95%CI:2600-3300人)、

女6900人(95%CI:6400-7500人)、総数9900人(95%CI:9100-10700人)と推定

1次調査用紙

多発性硬化症
患者数全国一次調査用紙

記載者氏名 _____
 施設名 _____
 食診療科名 _____
 所在地 _____
 記載年月日 平成15年__月__日

患者の有無	なし 0.		
	あり	1. 剖検確認例 2. 典型的に診断確定なMS 3. 視神経脊髄炎 (Devic病) 4. MS疑い 5. 分類不能	男: ___例 女: ___例 男: ___例 女: ___例 男: ___例 女: ___例 男: ___例 女: ___例 男: ___例 女: ___例

記入上の注意事項

食診療科における過去1年間(平成15年1月1日~平成15年12月31日)の患者数(新入院、繰越入院、新来、再来患者のすべて)について御記入下さい。
 1 全国受療者数推計を行いませんので、該当患者のない場合も なし(0)として御返送下さい。
 2 平成16年2月末日までに御返送いただければ幸いです。
 後日各症例について第二次調査を行いますので、御協力下さい。

解 説

<目的>

- ・ 全国の多施設を対象に多発性硬化症の患者数の推計する
- ・ 二次調査によって得られた結果から臨床疫学像を明らかにする

<方法>

- ・ 対象を2003年1年間の受療患者とし、2004年1月に患者数推計のための1次調査と臨床疫学像の把握のための2次調査を実施
- ・ 診療科別に無層化作為抽出した計6708科に送付

<結果>

- ・ 報告患者は3978人であり、男3000人(95%CI:2600-3300人)、女6900人(95%CI:6400-7500人)、総数9900人(95%CI:9100-10700人)と推定
- ・ 現在、1919人の2次調査のデータ入力を終了

<結論>

- ・ 患者数は9900人と推定された
- ・ 今後臨床疫学像を明らかにする予定である

MSにおける *Helicobacter pylori* 感染の意義

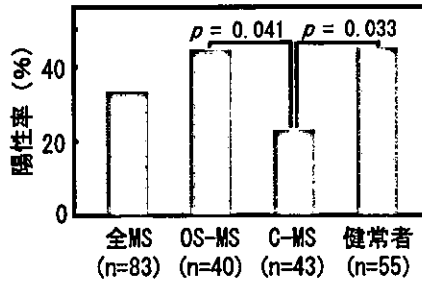


図1 抗HP-IgG抗体陽性率

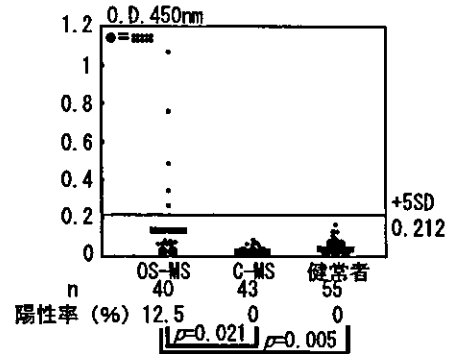


図2 抗HP-NAP-IgG抗体

- ・抗HP抗体陽性率は、C-MSで有意に低い(図1)
- ・C-MSにおいて、抗HP抗体陽性者は陰性者に比べ総合障害度(EDSS)が低い
- ・HPの産生するNAPに対する抗体は、OS-MS患者のみで認められた(図2)

OS-MS: 視神経脊髄型多発性硬化症、C-MS: 通常型多発性硬化症

解説

<目的>

- ・ *Helicobacter pylori* (HP) は、全人類の約50%に感染が認められる。HPは感染胃粘膜で好中球を活性化しうる菌体由来のneutrophil activating protein (HP-NAP)を産生する。本研究では日本人MSにおけるHP感染率を解明することを目的とした。

<方法>

- ・抗HP抗体、抗HP-NAP抗体の測定を行った。
- ・対象はMS 83名(OS-MS 40名、C-MS 43名)、健常者55名。

<結果>

- ・抗HP抗体陽性率は健常者45.5%、OS-MS45.0%、C-MS23.3%であり(図1)、C-MSは健常者やOS-MSに比べ有意に陽性率が低下していた。
- ・C-MSにおいてEDSSは陰性群で4.9、陽性群で2.9と陽性者において低下する傾向がみられた。
- ・抗HP-NAP抗体はOS-MSの12.5%で陽性だが、C-MSや健常者では全例陰性であった(図2)。

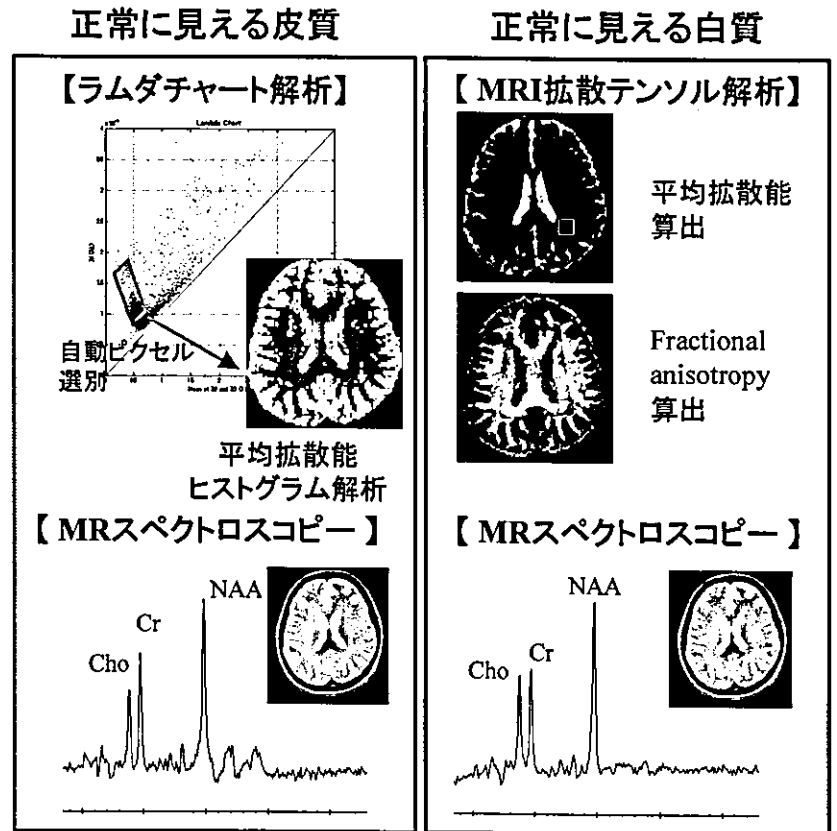
<結論>

- ・C-MSで健常者やOS-MSに比べHPの感染率が低下していた。
- ・その機序として下記の要因が考えられた。
 - 1) 生活の近代化による環境の変化
 - 2) HP感染自体にMSを抑制する作用がある

3テスラMRI/MRSを用いた MS患者大脳皮質・白質非侵襲的機能評価

●3テスラMR機を用いて、「一見正常に見える」MS患者における大脳皮質・白質の機能評価を行う手法を開発した。

●この機能評価法により算出されたパラメータを利用して、MSの病態解明や機能的予後の推定、治療法を選択などに有用な情報を発症早期から非侵襲的に得ることが可能となった。



解 説

- ・MSでは、通常の画像診断では「一見正常に見える」大脳白質および皮質にも発症早期から病的所見が認められる。これらの所見はMSの診断確定や予後推定およびそれらに基づいた治療法を選択のうえできわめて有用な情報を与えてくれる。
- ・われわれは、3テスラMR機を用いて、MRI拡散強調画像や¹H-MRスペクトロスコピーによりMS患者大脳皮質・白質の機能評価をより客観的に行う手法を開発した。
- ・結果
 - 1) 二次進行型MSのみならず再発寛解型MSにおいても大脳皮質障害が認められた。
通常のMRI画像で異常所見を認めない段階で大脳皮質障害が生じている可能性がある
 - 2) 視神経脊髄型MSにおいても、通常型MSと同様に一見正常に見える大脳皮質・白質で病的変化が生じており、通常型MSと同様の病態が大脳に生じている可能性がある。

日本人MSにおける候補遺伝子関連研究

疫学的背景、免疫学的、
病理学的、生化学的見
地からの発症機構に関
する知見を参考に候補
遺伝子を選出しSNPに
ついて検討



多発性硬化症疾患感受性
遺伝子の同定



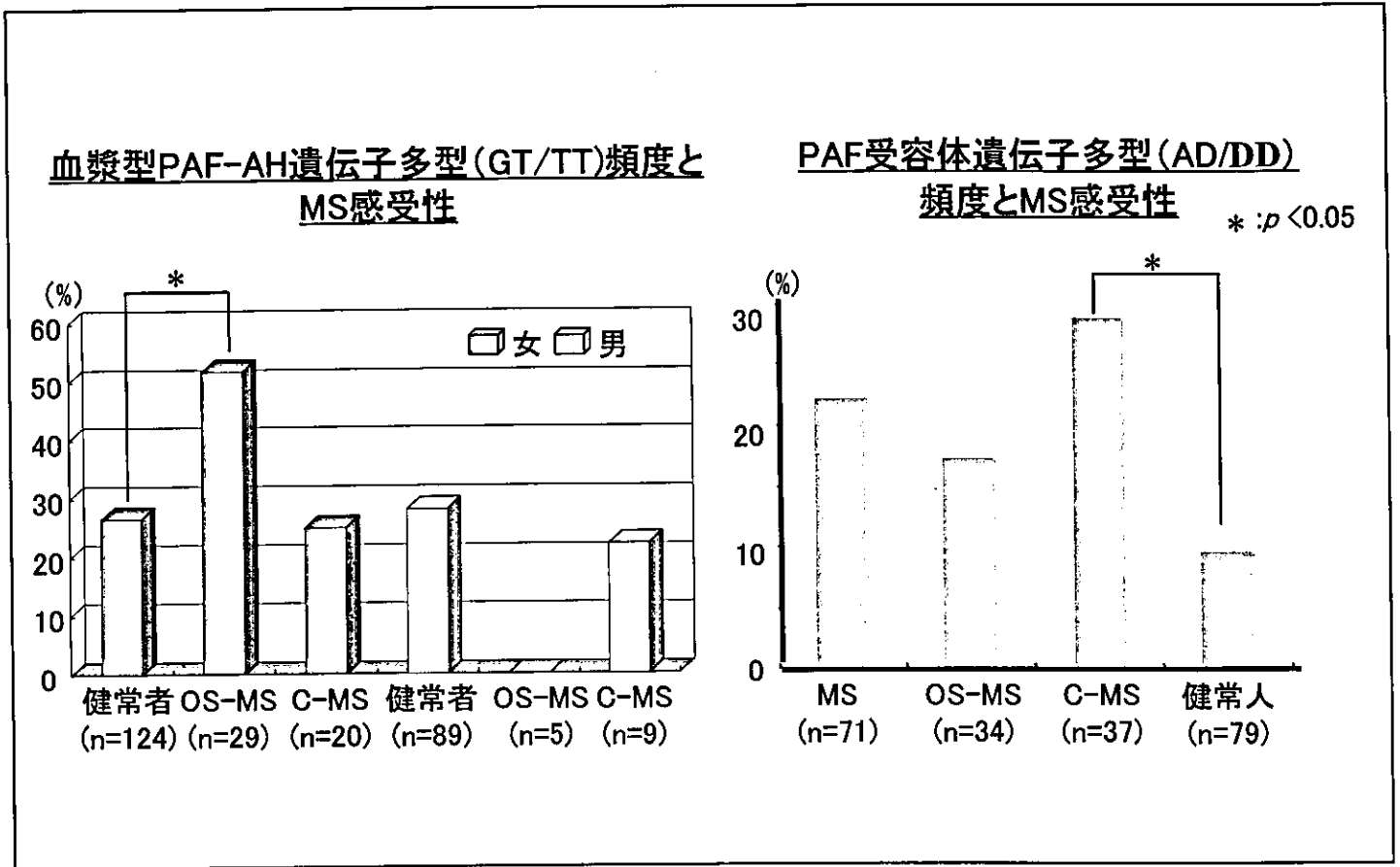
多発性硬化症の病態解明
臨床像，薬剤効果，副作
用を考慮したオーダーメ
イド医療

候補遺伝子	遺伝子産物の 免疫学的作用	MS病型	関連
HLA-DRB1*1501	抗原提示	通常型	感受性
HLA-DPB1*0501	抗原提示	OSMS	感受性
HLA-DPB1*0301	抗原提示	通常型 OSMS	感受性 抵抗性
CTLA-4	抑制	通常型	経過と関連
Vitamin D受容体 <i>Bsm</i> I	抑制	通常型	感受性
Vitamin D受容体 <i>Apa</i> I	抑制	通常型	感受性
Estrogen受容体 P allele	抑制	通常型	感受性
Estrogen受容体 Xx型	抑制	通常型	発症年齢と関連
OPN 8090 C/T	調整	通常型	感受性
OPN 9250 T/C	調整	通常型	なし
OPN 9583 A/G	調整	通常型	発症年齢と関連
Apo E		通常型	なし
CCR2 64I	抑制	通常型	抵抗性
TRAIL 1595C/T	調整	通常型	感受性

解 説

- ・MSは単一遺伝子疾患とは考えにくく、複数の遺伝子が関与する多遺伝子疾患である。疾患感受性遺伝子を同定するため患者・対照群の候補遺伝子関連研究を行った。
- ・候補遺伝子を選出しSNPについて検討し、MS疾患感受性遺伝子の同定を行い、MSの病態解明およびオーダーメイド医療の実現を目的とした。
- ・DRB1*1501は通常型MS、DPB1*0501はOSMS、DPB1*0301は通常型MSの感受性遺伝子である。
- ・ビタミンD受容体遺伝子、エストロゲン受容体遺伝子、オステオポンチン遺伝子、ケモカインレセプター2遺伝子、TRAIL遺伝子変異が疾患感受性遺伝子、またCTLA4遺伝子はMSの経過や重症度に影響を与える遺伝子変異であることを指摘した。

血漿型PAF-AHおよびPAF受容体遺伝子多型とMS感受性



解 説

<目的>

- ・日本人MSにおける血漿型PAF-AHおよびPAF受容体遺伝子多型の頻度を明らかにする

<方法>

- ・血漿型PAF-AH遺伝子多型($G^{994} \rightarrow T$)、PAF受容体遺伝子多型($A^{224} \rightarrow D$)をPCR-RFLP法を用いて決定し、OS-MS、C-MSおよび健常対照においてその頻度を比較

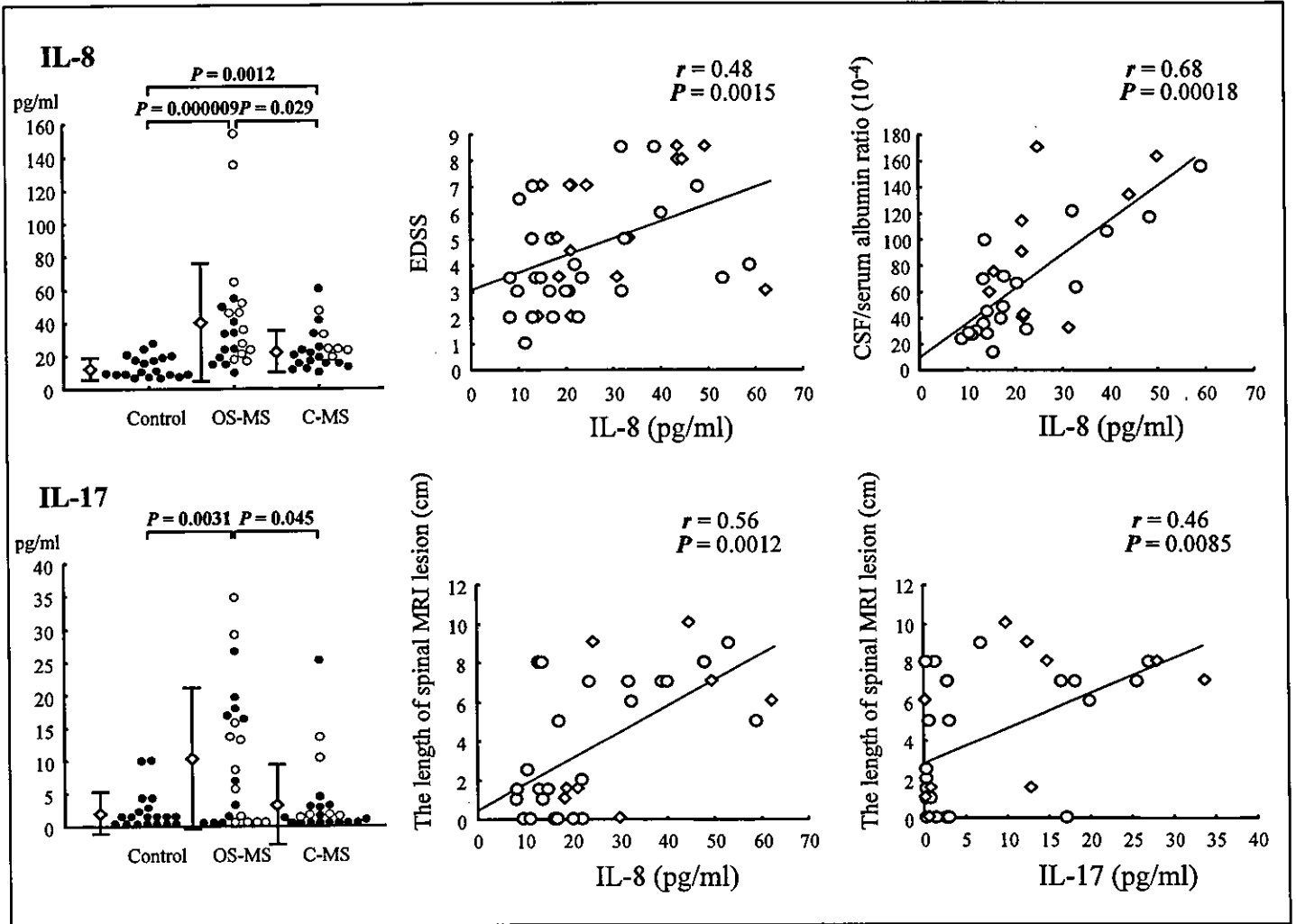
<結果>

- ・血漿型PAF-AH遺伝子多型頻度(GT/TT)はOS-MS、C-MSおよび健常群にて明らかな差異はみられなかったが、女性において重症型OS-MSでは健常群と比べ、GT/TTの遺伝子型が有意に高かった
- ・PAF受容体遺伝子多型頻度(AD/DD)はC-MSにおいて健常群と比べ、有意に多かった

<結論>

- ・OS-MSの重症化に血漿型PAF-AH遺伝子多型が、C-MSの発症にPAF受容体遺伝子多型が関与している可能性が考えられた

MS髄腔内でのIL-17/IL-8系の活性化： 16種のサイトカイン・ケモカインの多項目同時測定法の開発



解 説

視神経脊髄型MS (OS-MS)と通常型MS(C-MS)の免疫病態の違いを明らかにする。

<方法>

- ・対象：再発期OS-MS 20名、再発期C-MS 20名、Control 19名
- ・16種の髄液サイトカイン・ケモカイン濃度 (IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12(p70), IL-13, IL-17, IFN- γ , TNF- α , G-CSF, MCP-1, MIP-1 β) を蛍光ビーズサスペンションアレイシステムで同時測定した。

<結果>

- ・OS-MSはC-MSに比し、IL-8, IL-17, IL-5が有意に高値であった。
- ・各サイトカイン・ケモカインの中では、IL-8, IL-17濃度のみが、EDSS、髄液蛋白濃度、髄液/血液アルブミン比、脊髄MRIでの病変長と有意な正の相関を認めた。

<結論>

- ・髄腔内でのIL-17/IL-8系の活性化はOS-MS特異的なサイトカイン変化であり、さらにOS-MSに特徴的な臨床所見と有意に相関している。
- ・IL-17/IL-8系の活性化は好中球の局所への動員に関与し、OS-MSでも同様の機序が起きている可能性がある。