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F. 知的所有権の出願・取得状況

1) 特許取得

①発明の名称；IL-17 産生抑制物質およびそのスクリーニング方法
発明者；大木伸司、三宅幸子、山村　隆　他一名
出願日；2007 年 2 月 28 日
出願人；財団法人ヒューマンサイエンス振興財団
出願番号または公開番号；出願準備中のためなし

②発明の名称；IL-17 に起因する炎症を改善するための医薬組成物
発明者；大木伸司、三宅幸子、山村　隆　他一名
出願日；2007 年 2 月 28 日
出願人；財団法人ヒューマンサイエンス振興財団
出願番号または公開番号；出願準備中のためなし

③特願 2005-329418　自己免疫疾患治療剤、およびその応用

④米国出願 11/266409 Method and

composition for treating multiple sclerosis
⑤国際出願 PCT/JP2006/322659　調節性T細胞の機能異常に基づく疾患の治療剤、およびその応用
⑥「神経細胞の細胞死阻害剤及びスクリーニング方法」公開番号 WO2007/088712
⑥HTLV-I 関連脊髄症の予防・治療剤およびアポトーシス促進剤　(特許出願中)
⑦特許出願 (2007-264623号) ；吉川弘明、丸田高広：ジヒドロピリジン受容体抗体レベルに基づく胸腺腫合併重症筋無力症の診断

2）実用新案登録

なし

3）その他

なし

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17年度～平成19年度)

研究成果解説資料 目次

20. 重症筋無力症の嚥下障害パターン
21. 抗 MuSK 抗体が神経筋伝達に及ぼす作用の検討
22. 抗 MuSK 抗体陽性重症筋無力症の発症機序の研究
23. 重症筋無力症と抗 Kv1.4 抗体
24. 重症筋無力症における新規標的抗原の探索
25. 重症筋無力症における胸腺異常－正常対照との質的差異－
26. 胸腺腫における AIRE の発現と重症筋無力症合併
27. 徳島大学病院における重症筋無力症 96 例の検討

Ⅲ. ギラン・バレー症候群(Guillain-Barre syndrome; GBS)・類縁疾患

28. ギラン・バレー症候群・CIDP の患者側因子としての CD1 遺伝子多型
29. Guillain-Barré 症候群における抗ガングリオシド抗体と抗ガングリオシド複合体抗体

Ⅳ. 慢性炎症性脱髄性多発神経炎(Chronic inflammatory demyelinating polyneuropathy; CIDP)・その他の慢性免疫介在性ニューロパチー

30. 慢性炎症性脱髄性多発根神経炎(CIDP)における中枢神経系病変の合併
31. CIDP の有病率・発症率と、長期予後
32. 多巣性運動ニューロパチー(MMN)の診断には伝導ブロックの証明が必須か？
33. Crow-Fukase 症候群に対する新規治療法の開発：自己末梢血幹細胞移植療法
34. 末梢神経における slow K+ channel の in vivo 評価法
35. 血液神経関門を構成する微小血管内皮細胞の高度に専門分化したバリア機能

Ⅴ. HTLV-1 関連脊髄症(HTLV-1-associated myelopathy; HAM)

36. HLA-A24 はウイルス量を減少させるが HAM 発症のリスクを上げる
37. HAM/TSP 患者末梢血における high HTLV-I proviral load には Integrin/ligand signaling の活性化が関与している

Ⅵ. 傍腫瘍性神経症候群・その他の抗神経抗体を介する神経疾患

38. 橋本脳症の臨床免疫学的検討
39. 抗 VGCK 抗体関連辺縁系脳炎

Ⅶ. 急性散在性脳脊髄炎(ADEM)・その他の関連する脳脊髄炎

40. 日本人における急性散在性脳脊髄炎の臨床像の解析と遺伝要因の関与の検討
41. 急性散在性脳脊髄炎(ADEM)における血液脳関門(BBB)機能
42. アトピー関連脊髄炎，末梢神経障害，平山病の病態解明と治療法の開発
43. 神経好中球病：脳炎・脳症・髄膜炎の新しいカテゴリー

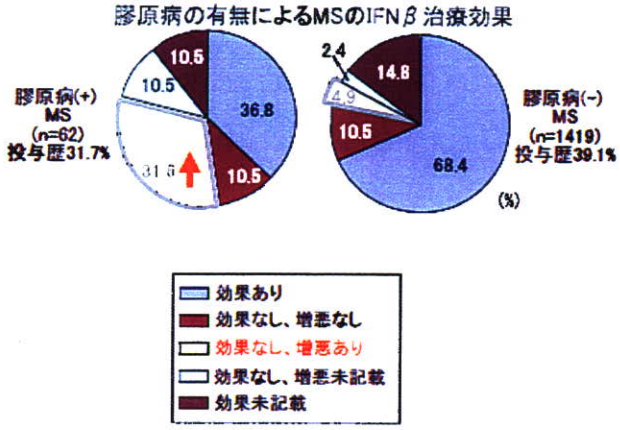
Ⅷ. 筋炎

44. 新基準での筋炎病型分類による血清サイトカインおよびDeath receptor 値の検討

Ⅸ. その他

45. Diagnosis procedure combination(DPC)制度下における免疫性神経疾患診療

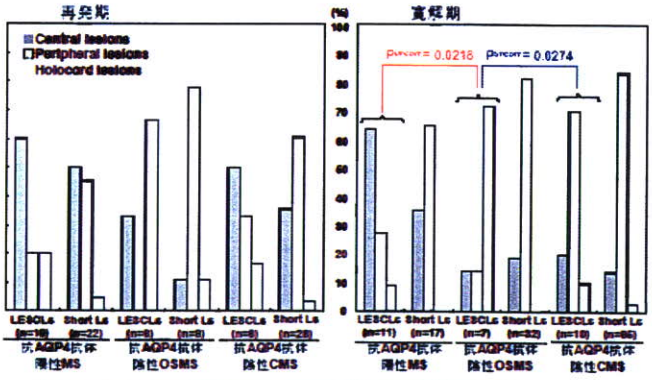
日本人MSの病像解析: 全国疫学調査と自検例



NMO診断基準を満たす抗AQP4抗体陽性MSとLESCLsを伴う抗AQP4抗体陰性OSMSの比較

	抗AQP4抗体陽性 MS/NMO (n=14)	抗AQP4抗体陰性 OSMS/LESCLs (n=18)
性別 (男 / 女)	0/14	4/14 (1 : 3.5)
発症年齢 (歳)	38.8 ± 14.6	33.9 ± 15.4
罹病期間 (年)	14.8 ± 9.2	14.0 ± 9.4
再発率 (回数 / 年)	1.2 ± 0.6*	0.8 ± 0.5*
EDSS score	5.6 ± 2.7	6.4 ± 2.3
重度の視神経炎 (≥ FS 5)	11/14 (78.6%)	15/18 (83.3%)
横断性脊髄炎	9/14 (64.3%)	15/18 (83.3%)
2次性進行型	0/14 (0.0%)	1/18 (5.6%)
髄液細胞増多 (≥ 50/μl)	2/14 (14.3%)	5/15 (33.3%)
OB	1/9 (11.1%)	2/16 (12.5%)
SSA/SSB	4/14 (28.6%)	2/12 (16.7%)
BarkhofのMRI診断基準	7/14 (50.0%)	4/18 (22.2%)
PatyのMRI診断基準	11/14 (78.6%)	8/18 (44.4%)
LESCLs	13/14 (92.9%)	18/18 (100.0%)

再発率
抗AQP4(+) MS/NMO > 抗AQP4(−) OSMS/LESCLs (有意差あり)
SSA/SSB, Barkhof/Paty MRI
抗AQP4(+) MS/NMO > 抗AQP4(−) OSMS/LESCLs (傾向あり)
* $P < 0.05$



抗AQP4 抗体陽性MS　：中心灰白質に限局
抗体陰性OSMS　：中心灰白質から辺縁白質を含む
抗体陰性CMS　：辺縁白質に限局　　＝ 短い病巣と同じ分布

自験MS症例でのMRI所見に基づく臨床像の比較

	LESCLs (+) OSMS (n=33)	LESCLs (+) CMS (n=23)	LESCLs (-) brain lesions (+) (n=33)	LESCLs (-) brain lesions (-) (n=32)
臨床病型 (OSMS / CMS)	33/0	0/23	3/30	14/18
性別 (男 / 女)	4/29 (1 : 7.3)	6/17 (1 : 2.8)	12/21 (1 : 1.8)	11/21 (1 : 1.9)
発症年齢 (歳)	37.3 ± 17.3	34.4 ± 12.8	28.9 ± 12.4	30.7 ± 12.1
罹病期間 (年)	13.2 ± 9.2	11.7 ± 8.3	10.7 ± 10.3	11.5 ± 9.6
再発率 (回数 / 年)	1.0 ± 0.7	0.7 ± 0.4	0.8 ± 0.7	0.7 ± 0.6
EDSS score	6.0 ± 2.5	5.3 ± 2.5	2.8 ± 2.5	2.0 ± 2.2
重度の視神経炎 (≥ FS 5)	28/33 (84.8%)	6/23 (26.1%)	7/33 (21.2%)	11/32 (34.4%)
横断性脊髄炎	26/33 (78.8%)	9/23 (39.1%)	2/33 (6.1%)	6/32 (18.8%)
2次性進行型	2/33 (6.1%)	7/23 (30.4%)	1/33 (3.0%)	1/32 (3.1%)
髄液細胞増多 (≥ 50/μl)	8/30 (26.7%)	0/23 (0.0%)	1/28 (3.6%)	1/29 (3.4%)
OB	3/27 (11.1%)	8/22 (36.4%)	16/27 (59.3%)	4/23 (17.4%)

* $P < 0.05$

OSMS/LESCLs(+)
再発率, 重度な視神経炎, 横断性脊髄炎, 髄液細胞増多
CMS/LESCLs(+)
横断性脊髄炎, 2次性進行型

解　説

〈目的,方法〉

MS全国臨床疫学調査と自検例の調査によりMSの病態を解明する

〈結果,結論〉

1. 全国臨床疫学調査:

a. 膠原病合併例は, 女性に多く, 高齢発症, OSMSの割合が高く, 長大な脊髄病変を有する割合が高い

b. IFNβ 治療では, 膠原病非合併例では効果が少ない可能性

c. 北ほどC-MSが多く, BarkhofのMRI診断基準を満たす割合が多い

d. 日本人MSの病像が西洋でのMSの病像に近づいている

2. 自検例での解析:

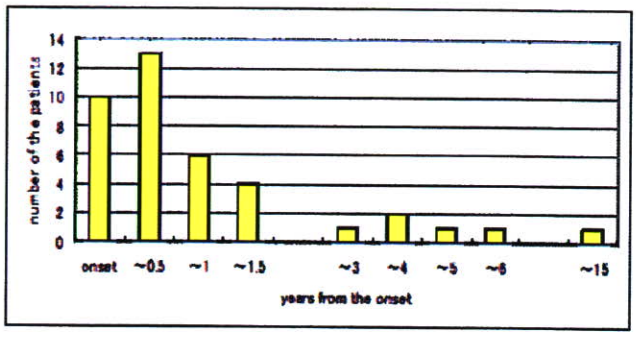
日本人MSには

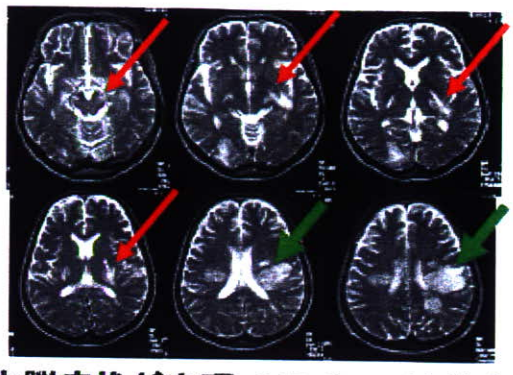
a. LESCLsを有する抗AQP4抗体陰性OSMSが存在し, LESCLsの分布やIFNβ-1bの治療効果において, 抗体陽性MS/NMOと異なる一群がある

b. LESCLの形成要因は抗AQP4抗体だけでなく多様性を持つと考えられた

c. HLAクラスIIに関連した亜群が存在する

Long spinal cord lesionsを呈した多発性硬化症の臨床的研究





79例のLCL-MS中、70%で脳症状が出現し、44%では大脳症状が出現. 84%でLCLは発症1.5年以内に出現. 64%では最初の脊髄炎でLCLに.

脳症状を呈したLCL-MSの脳MRIの特徴は、1). 20 mm以上の長さに及ぶ脳幹から頭頂部にかけての長い病変を示す(赤矢印: 95%), 2). Cavityを示す(80%), 3). 長径が30 mm以上の大きさの脳病変を示す(緑矢印: 68%).

128例のRRMSで抗アクアポリン抗体を測定した結果、抗体と再発率および失明とが相関. LCLも抗体も存在せず、5年以上、視神経と脊髄に症状が限局している一群がいることが判明.

解　説

＜目的＞　3椎体以上の長い脊髄病変を有する多発性硬化症(Neuromyelitis optica: NMO)の臨床特徴を明らかにする。

＜方法＞　McDonaldの診断基準多発性硬化症を対象に、臨床症状およびMRI所見、新潟大学脳研究所神経内科・田中恵子准教授との共同研究で、NMOに特異的な抗アクアポリン4抗体を測定し、抗体と臨床症状との関連について検討した。

＜結果＞　79例のLCL-MS中、70%で脳症状が出現し、44%では大脳症状が出現. 84%でLCLは発症1.5年以内に出現. 64%では最初の脊髄炎でLCLが出現した.脳症状を呈したLCL-MSの脳MRIの特徴は、1). 20 mm以上の長さに及ぶ脳幹から頭頂部にかけての長い病変を示す, 2). Cavityを示す(80%), 3). 長径が30 mm以上の大きさの脳病変を示す. 128例のRRMSで抗アクアポリン抗体を測定した結果、抗体と再発率および失明とが相関. LCLも抗体も存在せず、5年以上、視神経と脊髄に症状が限局している一群がいることが判明した.

＜結論＞　LCLは発病早期に出現し、多くのLCL-MS患者は脳症状を呈することが判った。また、LCLも抗アクアポリン4体も存在せず、5年以上、視神経と脊髄に症状が限局している一群がいることが判明し、OSMSとNMOは同一ではないことが示された.