入を増やし，シナプス小胞からのアセチルコリン放出を増強させるとされる．DAP は血液脳関門の通過が不良であるため，痙攣などの副作用は少ないが，大量投与で口周囲や手指のしびれ，痙攣，喘息発作，消化管の蠕動亢進，不整脈などを生じることがある．DAP は 10 mg を分 3 または分 4 で投与し，症状に合わせて 2 週毎に 5 mg ずつ増量する．DAP の効果は 20 分後から出現し 4 時間くらい持続する．

また，グアニジンもミトコンドリアなどの細胞内小器官へのカルシウム取り込みを抑制することにより，細胞内カルシウム濃度を上昇させる．通常 5〜10 mg/kg/日で開始し，3 日毎に増量して 30 mg/kg/日程度で維持することが多いが，骨髄抑制，腎尿細管性アシドーシス，慢性間質性腎炎，心伝導障害，肝障害，膵臓障害，末梢神経障害，精神症状などの副作用が知られている．Pyridostigmine などの抗コリンエステラーゼ薬も，弱いながら LEMS の症状を改善させるが，重症筋無力症での改善効果に比べて乏しい．しかし口渇などには有効である．DAP あるいはグアニジンと抗コリンエステラーゼ薬を併用することで，効果が増強する．

多くの場合，DAP に加えて，副腎皮質ホルモン，免疫抑制剤，血漿交換療法，IVIG 療法が選択される．Maddison ら[12]は SCLC を伴わない LEMS の 47 例を 1.3〜17 年追跡した結果を報告している．ほとんどの例で副腎皮質ホルモンに加え azathioprine，cyclosporin あるいは methotrexate を長期間併用しており（平均 6 年），治療により 88%で筋力改善がみられ，52%で VGCC 抗体価が低下，治療後 2 年で CMAP が 2.7 mV から 8.8 mV に改善した．症状の寛解を維持できたのは 43%であったが，免疫抑制剤を必要としなかったのはその 1/5 にとどまる．また，治療前の抗体価や CMAP の振幅と予後との関連はみられず，初期の筋力低下の程度が予後に関連した．

一般に，悪性腫瘍に伴う LEMS は，腫瘍の治療が良好に経過した場合，それに伴って LEMS の症状も改善することが多いが，自己免疫病としての LEMS は比較的長期間，免疫抑制療法が継続されることが多い．

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<田中惠子>

18. Isaacs 症候群治療の第1選択は

1 序論

Isaacs 症候群は，全身麻酔や睡眠時にも持続する筋硬直や手指の開排制限などの筋収縮後の弛緩障害(neuromyotonia)，および筋線維束性収縮などの末梢神経の持続性過剰興奮を主徴とする疾患である．筋電図では末梢神経遠位部起源と考えられる myokymic discharge や neuromyotonic discharge を伴う．本症候群においては，抗 voltage-gated K^+ channel（電位依存性カリウムチャネル: VGKC)抗体がその病態に関与している[1]．さらに近年では，中枢神経系の神経過剰興奮症状を伴う Morvan 症候群および辺縁系脳炎の一部にも，抗 VGKC 抗体の関与が明らかになっており，これらは immune-mediated potassium channelopathies として捉えられるようになった[2]．

2 指針

末梢神経系の過剰興奮が主体の Isaacs 症候群や，より臨床症状の軽い cramp-fasciculation 症候群の場合は，対症療法的に抗てんかん薬で症状をコントロールし，難治例では，血漿交換を施行する．Morvan 症候群や抗 VGKC 抗体陽性辺縁系脳炎例では，ステロイド療法や免疫グロブリン大量療法（IVIG）が考慮される（図1）．重症筋無力症（MG）合併例や傍腫瘍性症候群例では，原疾患の精査・加療に努めることも重要である．

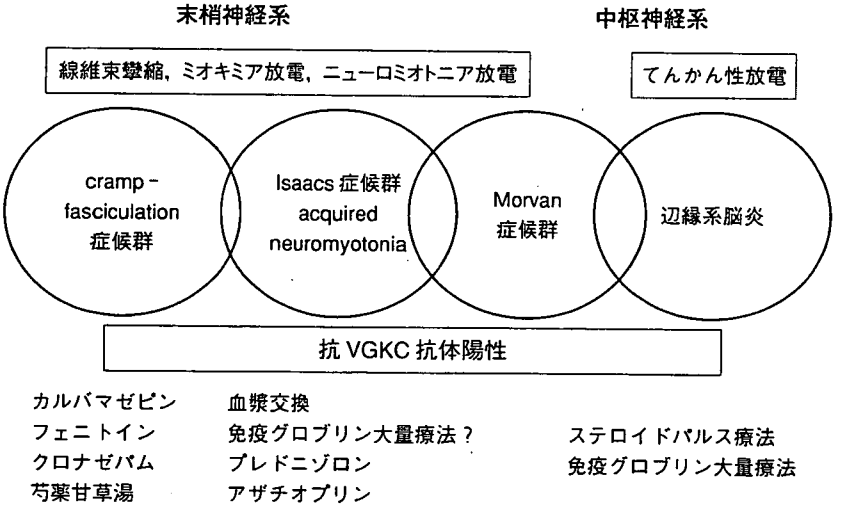

図1 神経系における免疫関連 K^+チャネル疾患治療のまとめ

JCLS 498-12826

3 エビデンス

Isaacs 症候群をはじめとする immune-mediated potassium channelopathies はいずれもまれな疾患で，RCT などのエビデンスはない．いずれも 1 例から数例の症例報告であるが，疾患ごとに概説する．

1 cramp-fasciculation 症候群および Isaacs 症候群（acquired neuromyotonia）

電気生理学的に myokymic discharges の有無で両症候群が鑑別されるが（表 1），Isaacs 症候群のみならず，cramp-fasciculation 症候群でも抗 VGKC 抗体が高率に認められ，近年では，両症候群に質的な相違点はないと考えられている[3]．抗 VGKC 抗体陽性で，自己免疫関連と考えられる症例でも Na^+チャネルブロッカーであるカルバマゼピンやフェニトインなどの抗てんかん薬で緩解し，血漿交換などの免疫療法を必要としない症例も存在する[4]．難治症例では，血漿交換による抗 VGKC 抗体の除去が，有効である[5-8]．MG 合併例では，血漿交換後のステロイドとアザチオプリンの併用での後療法が推奨されている．

IVIG については，合計 5 例の使用経験が報告されているが[9-11]，1 例のみ著効，3 例で無反応，1 例では増悪している[9]．

表 1 immune-mediated potassium channelopathies の典型的臨床徴候

疾患	臨床徴候	筋電図所見
cramp-fasciculation 症候群	筋痙攣 筋線維束攣縮 筋硬直	spontaneous single MU*3 discharges fasciculations after-discharges
Isaacs 症候群	上記に加え： ミオキミア*1 偽ミオトニア*2 筋肥大 過剰発汗	上記に加え： spontaneous continuous MU discharges myokymic discharges*4 neuromyotonic discharges*5
Morvan 症候群	上記に加え： 幻覚 不眠症 気分変容	上記に同じ

*1ミオキミア：不規則で持続時間が長い小さな不随意運動で，一部の皮膚表面からさざ波が周囲に波紋状に伝わるような筋収縮．

*2偽ミオトニア：ミオトニア症候群と異なり，叩打ミオトニアを認めず，把握ミオトニアが認められる．

*3motor unit，運動単位

*4ミオキミア放電：不随意に反復的に発射する運動単位電位で臨床上ミオキミアを伴う．単一運動単位が一定の頻度（2～60 Hz）で 2～10 回放電し，この一群が 0.1～10 秒間で反復する．

*5ニューロミオトニー放電：突発性に生じる運動単位発射で，運動神経軸索に起因し，数秒間にわたって高頻度（150～300 Hz）の発射が認められるが，典型的な例では反復する活動電位の振幅が漸減する．

2 Morvan 症候群

Morvan 症候群は，neuromyotonia，発汗異常などの末梢神経興奮性亢進に加え，重篤な睡眠障害，幻覚などの中枢神経症状を伴う疾患であるが，Liguori らは，抗 VGKC 抗体を認め，血漿交換で緩解した 76 歳男性（剖検時に肺腺癌あり）を報告した[12]．一方，Bequet らは，筋痙攣，ミオキミア，全身性の筋線維束攣縮，発汗過多，および睡眠異常を認めた 35 歳男性で IVIG を行ったところ，症状の改善が半年間持続したと報告している[13]．

3 抗 VGKC 抗体陽性辺縁系脳炎

Buckley らが，2001 年に抗 VGKC 抗体が認められた辺縁系脳炎の 2 例で，1 例が血漿交換で緩解したと報告した[14]．彼女らは，さらに症例を集積し，抗 VGKC 抗体陽性辺縁系脳炎 10 例中，血漿交換＋IVIG＋ステロイド療法の 2 例で著効，IVIG＋ステロイドの併用 3 例で著効，血漿交換＋IVIG の併用療法（ステロイド未投与）2 例では，効果が認められなかったと報告した[15]．本邦においては，辺縁系脳炎 20 例のうち 9 例で抗 VGKC 抗体が認められた．その中の 4 例でステロイドパルス療法や IVIG が施行され，臨床症状の改善が認められた[16]．辺縁系脳炎の中で抗 VGKC 抗体が陽性であることは，免疫療法に反応性があることを示唆している[15]．

4 根拠となった臨床研究の問題点と限界

抗 VGKC 抗体に関連する疾患に対する臨床研究は，いまだ症例報告か，数例の review にとどまり，エビデンスレベルは低い．

5 本邦の患者に適応する際の注意点

血漿交換については，欧米の論文では，詳細な記載はないが，PPF とデキストランで置換する単純血漿交換が頻用されている[5]．本邦では，二重膜濾過血漿交換が有効であった症例報告がある[17]．また MG や Guillain-Barré 症候群に対して本邦で頻用され，未知の感染症の心配もなく，血漿蛋白の置換を必要としない免疫吸着による血漿交換でも有効例が報告されている[18]．まず，侵襲のより少ない免疫吸着法を選択し，それが無効な場合，二重膜濾過を選択すべきである．

6 コメント

抗 VGKC 抗体のルーチンアッセイは，^{125}I-alfa-dendrotoxin（αDTX）を用いた免疫沈降法が行われているが，検査法および αDTX の親和性特性から，検出できる抗体は，Kv 1.1，Kv 1.2 および Kv 1.6 に対する IgG に限られる．αDTX が結合しない Kv 1.x に対する抗体も存在することが明らかになっており[19]，また我々は，patch clamp 法を用いて，IgM 抗 VGKC 抗体をもつ症例も存在することを明らかにしてきた[20]．すべての VGKC サブユニットに対しての IgG および IgM 抗体を検出できる検査法の開発が期待される．

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<渡邊 修　有村公良>

C 感染症

1．細菌性髄膜炎のガイドラインは

❶ 序論

細菌性髄膜炎は neurological emergency に位置づけられ，最も重篤な細菌感染症の一つである．抗生剤の進歩にもかかわらず，初期治療が不十分な場合，死亡または高度後遺症が残存する場合があり，十分な根拠に基づく適切な初期治療を選択することがきわめて重要である．

❷ 指針

細菌性髄膜炎の診療においては，髄膜刺激症状や皮疹などの全身症状から早い時期に髄膜炎を認識し，早期診断および早期治療が大切である．診断にあたっては，腰椎穿刺による髄液検査の適応を判断し，腰椎穿刺の適応がなければ血液培養検査を施行し，経験的治療を開始する．腰椎穿刺の適応であれば，採取した脳脊髄液を基に迅速診断し，起炎菌同定を試みる．起炎菌が未確定であれば，年齢や基礎疾患などを考慮した起炎菌を想定し，経験的治療を行い直ちに投与開始する．起炎菌が同定（推定）された場合にはその菌に対する標的治療を行う．また，抗生物質投与とともに副腎皮質ステロイド療法の追加療法も考慮する．

❸ ガイドライン

(1) **英国感染症学会**（British Infection Society：BIS；http://www.britishinfectionsociety.org）[1]

1）細菌性髄膜炎の早期認識

点状出血・紫斑性の皮疹または髄膜刺激症状をもとに早い時期に細菌性髄膜炎と認識する．皮疹が欠如する非典型的な例が存在する．髄膜炎症例の最大30％に項部硬直を欠き，抗生物質の事前投与は病状を覆い隠すことがあるので注意が必要である．

2）重症度の評価と救急処置

気道確保とともに呼吸数，末梢血酸素飽和度，脈拍，血圧などの循環動態，尿排泄などの全身を評価するとともに，意識状態，局所神経症状，痙攣，うっ血乳頭などの神経学的所見を迅速に評価し，全身状態の管理に努める．

3）診断と治療

a）病状として髄膜炎菌性敗血症が優位であるとき

腰椎穿刺は施行せず，抗生剤の投与を行う．

b）病状として髄膜炎が優位であるとき

① 頭蓋内圧亢進またはショック状態や呼吸不全などがなければ腰椎穿刺を行う．腰椎穿刺後，直ちに抗生物質の静脈投与を行い，副腎皮質ステロイド剤の投与を考慮する．

② 急速に進行する皮疹，末梢循環不全（capillary refill time＞4秒，乏尿，収縮期血圧＜90

mmHg)，呼吸数＜8回/分以下または＞30回/分，脈＜40/分または＞140/分，pH＜7.3またはBE＜−5 mEq/l，白血球数＜4000/mm³，GCSが12点未満の意識障害または2点を上回る悪化，局所神経症状，持続性痙攣，徐脈および高血圧，うっ血乳頭の存在は，ショック状態，呼吸不全や頭蓋内圧亢進の切迫・悪化を示し，これらの危険徴候を認める際には腰椎穿刺は延期する．

③頭部CT：頭部CTの正常所見は頭蓋内圧亢進を除外しない．臨床的に腰椎穿刺の禁忌事項がなければ，頭部CTは必須ではない．

4）治療

a）抗生物質

第3世代セフェム系抗生物質(cefotaxime あるいは cefotriaxone)の静脈投与を行い，55歳以上の高齢者にはリステリア菌治療を考慮しampicillin静脈投与を追加すべきである．また，ペニシリン耐性肺炎球菌である可能性が考慮された時にはvancomycine±rifampicinを適宜追加する．

b）副腎皮質ステロイド

抗生物質の投与の直前または同時にdexamethazoneを0.15 mg/kgを6時間毎・4日間の投与を推奨している．ただし，適切な抗生物質投与を確信していない時には本剤は使用しない．また，非細菌性髄膜炎が確定された場合には投与を中止する．

(2) 米国感染症学会 (Infectious Disease Society of America: IDSA; http://www.idsociety.org/)[2]

1）早期認識

髄膜炎症候群を早い時期から認識し，細菌性髄膜炎を考慮し迅速な診断，急性期の治療が重要である．

2）診断

a）腰椎穿刺の適応

免疫不全状態，中枢疾患を有する患者，新たに起こった痙攣，うっ血乳頭，意識障害あるいは神経脱落所見を認めた際には，腰椎穿刺前に頭部CTを施行し，頭蓋内占拠病変の有無の確認が推奨される．

b）細菌性髄膜炎の診断

①髄液所見ならびに起炎菌同定のための諸検査

細菌性髄膜炎では脳脊髄圧初圧亢進，髄液概観の変化，好中球増多，髄液糖の低下，髄液蛋白上昇を認める．細菌培養は陽性となるが，起炎菌確定までには48時間要するため，グラム染色やラテックス凝集反応による迅速検査が考慮される．PCR法は細菌DNAを増幅し起炎菌を同定する方法で，90%以上の感度および特異度を有する検査法である．さらに，広域的PCR法は細菌性髄膜炎診断のほか，除外診断，耐性菌検出や抗生剤投与継続の是非の決定にも有用かもしれない．Limulus lysate assay（カブトガニ抽出液を使用したエンドトキシン測定）はグラム陰性細菌感染症に応用されているが，細菌性髄膜炎の診断においては感度および特異性も十分でなく，テスト陰性結果はグラム陰性髄膜炎診断を除外しないためルーチン検査としては

推奨しない.

② ウイルス性髄膜炎との鑑別

市中における細菌性髄膜炎では髄液中の乳酸濃度測定は推奨しないが，脳外科術後の患者において髄液中の乳酸濃度が 4 mmol/*l* 以上であれば，抗生物質治療の開始を考慮すべきである．血清 CRP 正常値は細菌性髄膜炎の否定予測因子であるため，グラム染色の結果が陰性であり抗生剤投与の差し控えを考慮する患者において，血清 CRP 測定は有用となるかもしれない．血中プロカルシトニン濃度の上昇は細菌性髄膜炎診断において感度，特異度も良好であるが，検査自体が普及していないため，現時点では推奨しない．

3）治療

a）抗生物質

① 投与開始時期

抗生物質の投与開始時期については後方視的に検討されており，細菌性髄膜炎を neurological emergency と捉え，細菌性髄膜炎が疑われた時点でできるだけ早期に適切な加療が開始されるべきである．

② 適切な抗生物質の選択

細菌性髄膜炎の診断が下された後は，グラム染色の結果から推定される起炎菌に対する標的治療（表 1）を開始する．初期治療においては耐性菌の可能性を想定すべきであり，幼児・小児において，あるいは一部の専門家からは成人においても，第 3 世代セフェム系抗生物質（cefotaxime あるいは cefotriaxone）の投与に加え vancomycin 併用が推奨されている．髄液検査未施行患者やグラム染色結果が陰性の場合は，発症年齢や病状を考慮し，十分な根拠に基づく適切な経験的治療（表 2）を開始する．起炎菌や薬剤感受性が同定されれば，これらを基に最適治療に修正する．

表 1 成人における細菌性髄膜炎のグラム染色による推定起炎菌に対する推奨抗生物質
（文献 2 著者改変）

起炎菌	推奨治療薬	第 2 選択薬
Streptococcus pneumoniae	vancomycin＋third-generation cephalosporin[b,b]	meropenem, fluoroquinolone[c]
Neisseia meningitidis	third-generation cephalosporin[a]	penicillin G, ampicillin, chloramphenicol, fluoroquinolone, aztreonam
Listeria monocytogenes	ampicillin[d]あるいは penicillin G[d]	trimethoprim-sulfamethoxazole, meropenem
Streptococcus agalactiae	ampicillin[d]あるいは penicillin G[d]	third-generation cephalosporin[a]
Haemophilus influenzae	third-generation cephalosporin[a]	chloramphenicol, cefepime, meropenem, fluoroquinolone
Escherichia coli	third-generation cephalosporin[a]	cefepime, meropenem, aztreonam, fluoroquinolone, trimethoprim-sulfamethoxazole

[a] ceftriaxone あるいは cefotaxime
[b] ある専門家は dexamethazone 投与時には rifampicin を追加投与する．
[c] gatifloxatin あるいは moxifloxacin
[d] アミノグリコシド系の追加考慮

表 2 年齢と病態に基づいた細菌性髄膜炎の経験的治療のための推奨抗生物質（文献 2 改変）

基礎因子	起炎菌	抗菌療法
年齢		
＜1 カ月	*Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*, *Klebsiella species*	ampicillin＋cefotaxime あるいは ampicillin＋aminogycoside
1～23 カ月	*Streptococcus pneumoniae*, *Neisseria meningitidis*, *S. agalactiae*, *Haemophilus influenzae*, *E. coli*	vancomycin＋third-generation cephalosporin[a,b]
2～50 歳	*N. menigitidis*, *S. pneumoniae*	vancomycin＋third-generation cephalosporin[a,b]
＞50 歳	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, 好気性グラム陰性桿菌	vancomycin＋ampicillin＋third-generation cephalosporin[a,b]
頭部外傷		
脳底部頭蓋骨骨折	*S. pneumoniae*, *H. influenzae*, A 群 β 溶血性連鎖球菌	vancomycin＋third-generation cephalosporin[a]
穿通外傷	*Staphylococcus aureus*, コアグラーゼ陰性ブドウ球菌（*Staphylococcus epidermidis*），好気性グラム陰性桿菌（*Pseudomonas aeruginosa*）	vancomycin＋cefepime，vancomycin＋ceftazidime あるいは vancomycin＋meropenem
脳外科手術後	好気性グラム陰性桿菌（*P. aeruginosa*），*S. aureus*，コアグラーゼ陰性ブドウ球菌（*S. epidermidis*）	vancomycin＋cefepime，vancomycin＋ceftazidime あるいは vancomycin＋meropenem
CSF シャント	コアグラーゼ陰性ブドウ球菌（*S. epidermiids*），*S. aureus*，好気性グラム陰性桿菌（*P. aeruginosa*），*Propionibacterium acnes*	vancomycin＋cefepime[c]，vancomycin＋ceftazidime[c] あるいは vancomycin＋meropenem[c]

[a] ceftriaxone あるいは cefotaxime

[b] ある専門家は dexamethazone 投与時には rifampicin を追加投与する．

[c] 幼児や小児では，グラム染色でグラム陰性桿菌が検出されなければ vancomycin 単独でもよい

- cephalosporins：第 3 世代セフェム系は薬剤感受性を有する髄膜炎菌性および肺炎球菌性髄膜炎に推奨され，好気性グラム陰性桿菌性髄膜炎にも効果的である．しかし耐性菌が増加しており，感受性試験は治療にとって重要である．ceftazidime は緑膿菌性髄膜炎への効果が示されている．第 4 世代セフェム系である cefepime は，小児における細菌性髄膜炎において cefotaxime と同様の安全性と効果が示されており，また，in vitro においてエンテロバクター菌や緑膿菌に対して第 3 世代セフェム系より優れた効果が示されている．
- vancomycin：本剤の投与はペニシリンやセフェム剤感受性菌に対しては推奨されない．高度耐性菌に対しては第 3 セフェム系と併用療法すべきであり，単独投与はすべきではない．本剤使用においては血中濃度（トラフ値）を 15～20 μg/m*l* に維持することが望ましい．
- rifanpin：臨床データが不足しているものの，一部の専門家は高度耐性の肺炎球菌性髄膜炎に対して第 3 世代セフェム系±vancomycin 治療と併用するだろう．本剤の使用は，起炎菌に対して感受性があり，臨床的および細菌学的に予測より治療効果の遅延を認めた際に併用すべきである．また，本剤はブドウ球菌性の CSF シャント感染に vancomycin と併用すべきで

ある.

- carbapenems: imipenem は痙攣誘発が高頻度でありその使用は推奨しない. meropenem は第3セフェム系と同等の効果があり，第2選択薬として推奨できる．高度耐性の肺炎球菌に対しては第2選択薬として有効ではないかもしれないが，標準療法耐性のグラム陰性菌に対しては有効であるかもしれない.
- fluoroquinolones: 本剤の使用は二次選択として限定し，多剤耐性グラム陰性桿菌や標準療法に反応がみられないか，または，使用不可の場合にのみ投与すべきとしている.

③ 治療期間

抗生物質の治療期間は科学的根拠に基づくというより習慣的なものであるが，起炎菌ごとの治療期間が示されている.

b）副腎皮質ステロイド

成人においては，抗生物質初回投与の10分から20分前か，少なくとも同時に dexamethazone（0.15 mg/kg）を6時間毎に2日から4日間の投与が推奨されている．本剤は肺炎球菌性髄膜炎が疑われた症例や確認された症例において開始すべきであり，グラム染色によるグラム陽性双球菌の確認または血液，髄液培養で肺炎球菌が確認された場合にのみ継続すべきである．すでに抗生物質が投与されている場合には予後改善の期待が少ないため，同剤は投与すべきではない．また，一部の専門家からは，成人のすべての症例に投与すべきとしているが，他の起炎菌による髄膜炎における治療効果についてはデータが不十分である.

4 本邦の患者に適応する際の注意点

米国においては耐性菌の増加は，英国やオランダにおける耐性菌の検出頻度よりもはるかに高率であり，ガイドラインにおいても英国および米国においての抗生物質の第1選択薬に相違がみられる．本邦の成人例の細菌性髄膜炎の主要起炎菌は肺炎球菌が最も頻度が高く，次いでブドウ球菌である．近年，本邦においても耐性菌の検出が増加しており，特にペニシリン耐性肺炎球菌の増加には留意する必要がある．この状況は米国の状況と同様であり[3]，本邦においても耐性菌を考慮した初期治療の選択が重要と思われる．また，成人における細菌性髄膜炎の実際の薬剤投与量や投与方法については，薬物動態を考慮し，ペニシリン系，セフェム系およびカルバペネム系は静脈的に分割投与を行い，髄液濃度を急速に上げ維持することが重要である．本邦における薬剤投与についての明確な基準は存在していないが，実際には保険適応範囲内より大量の薬剤を要することがある.

5 コメント

細菌性髄膜炎の頻度は他臓器の細菌感染症に比べ頻度が少ない上，二重盲検ランダム化比較試験が少なく，その治療ガイドラインは専門家の経験的な治療に立脚している．本症の急性期においては，起炎菌が未確定で経験的治療が必要な場合が多いが，各医師の経験に基づく治療法ではなく，ガイドラインに従い適切な初期治療を選択することがきわめて重要である.

最後に，本邦においても日本神経学会，日本神経治療学会，日本神経感染症学会の3学会合同による細菌性髄膜炎の診療ガイドラインの作成が始まっており，日常診療での活用が期待さ

れる.

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Discrimination of Antibody to Herpes B Virus from Antibody to Herpes Simplex Virus Types 1 and 2 in Human and Macaque Sera[▽]

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The antigenic cross-reactive characteristics of herpes B virus and herpes simplex virus (HSV) type 1 (HSV-1) and HSV-2 are responsible for false-positive diagnoses by serological assays in humans and macaques. In the present study, we developed a fluorometric indirect enzyme-linked immunosorbent assay (ELISA) with recombinant herpes B virus glycoprotein D (gD) and HSV-1 and HSV-2 gG (gG-1 and gG-2, respectively) to discriminate between the three primate herpesvirus infections. The secreted form of gD, gDdTM, was used to detect antibody to herpes B virus gD. Sera positive for herpes B virus, HSV-1, and HSV-2 showed specific reactions to gD, gG-1, and gG-2, respectively. Sera collected from humans and rhesus macaques were investigated for the presence of antibodies to the recombinant proteins of the three herpesviruses. The results suggested that the approach is able to discriminate between herpes B virus and HSV infections. The ELISA was also found to be able to detect infections with multiple primate herpesviruses and may have the potential to identify a subsequent infection in individuals that have already been infected with another herpesvirus. In addition, we found evidence of a greater cross-reactivity of herpes B virus with HSV-1 than with HSV-2. It is suggested that the ELISA with the recombinant antigens is useful not only for the serodiagnosis of primate herpesvirus infections but also for elucidation of the seroprevalence of herpesviruses in humans and primates.

Herpes B virus (*Cercopithecine herpesvirus* 1) infection is a fatal zoonosis characterized by acute encephalomyelitis (26, 27). The rate of mortality among individuals with the infection is high if such individuals are not given antiviral therapy in the early stages of infection. The natural hosts of the causative agent are Asian macaques, which are used in the medical field as models for humans. This suggests that laboratory workers in contact with the macaques could become exposed to virus-contaminated sources, such as saliva and urine from infected hosts (4). Therefore, the development of a rapid and accurate method for the detection of herpes B virus infection is required for both the early diagnosis of the infection in patients and the establishment of virus-free macaque colonies. Serological assays, including enzyme-linked immunosorbent assay (ELISA) and Western blotting (WB) analysis with a herpes B virus-infected cell antigen, are available for the detection of herpes B virus infections (2, 7, 12, 18).

The serodiagnosis of herpes B virus infections is difficult because of the antigenic cross-reactivity of herpes B virus with related herpesviruses. Herpes B virus is classified as a member of the subfamily *Alphaherpesvirinae*, which includes herpes simplex virus (HSV) type 1 (HSV-1) and HSV-2, and has been shown to share antigenic and biological characteristics with these human herpesviruses, such as a tropism for neurons and propagation and dissemination in natural hosts (6, 8, 21). The high seroprevalence of HSV in humans, which has been reported to be 60 to 88% for HSV-1 (3, 5, 28, 29), limits the detection of herpes B virus infection by serological tests in patients suspected of being infected with the virus. In addition, a biosafety level 4 laboratory is required for preparation of the virus-infected cell antigen. Therefore, an alternative antigen as a replacement for the infected cell antigen is needed for the serological diagnosis of herpes B virus infections.

Recombinant DNA techniques currently play an important role in the diagnosis of many viral infections. The recombinant proteins used as antigens in serological tests are particularly useful for the discrimination of antibodies to closely related viruses. Immunoassays with glycoprotein G (gG) of HSV-1 and HSV-2 (gG-1 and gG-2, respectively), which are known to be type-specific antigens (16, 25), have been developed for the typing of HSV (1, 9, 14, 15, 22) and are available commercially. These assays have been applied in epidemiological studies as well as to the serological diagnosis of infections in patients. In addition, the development of serological assays for the diagnosis of herpes B virus infection with the recombinant protein has been reported (20, 24). In an earlier study we produced the

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gD of herpes B virus in mammalian cells; and the resultant recombinant protein was evaluated for its antigenicity by WB, dot blotting, and immunoprecipitation analyses (24). Since a nonspecific reaction was observed by WB, we constructed the secretory form of gD, gDdTM, which lacked the transmembrane domain (TM) and cytoplasmic tail (CT). gDdTM showed a specific reaction with sera from herpes B virus-infected macaques and was confirmed to have the same sensitivity as the original gD antigen. Therefore, we concluded that the gDdTM antigen is useful for the detection of antibody to herpes B virus.

In the present study, we developed a fluorometric indirect ELISA with a combination of recombinant herpes B virus gD, gG-1, and gG-2 as coating antigens. We used the gDdTM described above to detect antibody to herpes B virus. The three antigens were investigated for their cross-reactivities with sera confirmed to have antibody to herpes B virus or HSV. Sera from rhesus macaques and humans, including patients with meningitis or myelitis, were also examined for the presence of antibody to herpes B virus, HSV-1, or HSV-2. The results were used to evaluate the ability of the ELISA to discriminate between the three herpesvirus infections.

MATERIALS AND METHODS

Antigens. The preparation of recombinant herpes B virus gDdTM has been described previously (24). A recombinant plasmid, pBgDdTM, was used to transfect COS7 cells. The supernatant containing the resultant gDdTM was used as a coating antigen, while the supernatant of the COS7 cells transfected with an empty vector, pcDNA3.1(−), was used as the negative coating antigen. The recombinant gG-1 and gG-2 antigens and the whole HSV-1 and HSV-2 antigens were purchased from Austral Biologicals and Biogenesis Ltd. (Poole, United Kingdom), respectively.

Serum samples. Polyclonal antisera with antibodies to HSV-1 and HSV-2 were collected from rabbits experimentally immunized with HSV-1 and HSV-2 (11). The complement fixation titers to HSV for the anti-HSV-1 and anti-HSV-2 rabbit sera were 1:256 and 1:128, respectively (10). Human control sera confirmed to have HSV-1 or HSV-2 antibody were also used for evaluation of the ELISA developed in the present study. The control serum sample for HSV-1 was obtained from a person with no clinical symptoms. This serum sample was confirmed to have a complement fixation titer to HSV of 128 (10) and neutralizing antibody titers to HSV-1 and HSV-2 of 64 and 4, respectively (13). Serum obtained from a patient with meningitis was used as the control for HSV-2 (17). Antibody to gG-2 was qualitatively detected in this patient's serum by a type-specific ELISA, and amplified products of HSV were obtained from the cerebrospinal fluid of this patient, although the virus type was not determined. Control serum with antibody to herpes B virus was obtained from a rhesus macaque that was naturally infected with the virus. The antibody to herpes B virus in this serum was qualitatively detected by ELISA with inactivated herpes B virus antigen (23). In addition, 24 and 21 serum samples were collected from rhesus macaques and persons with no clinical symptoms, respectively. Five convalescent-phase serum samples were obtained from patients diagnosed with central nervous system HSV infections (17).

Fluorometric indirect ELISA. Ninety-six-well microplates (Maxisorp immunoplate; Nalge Nunc, Tokyo, Japan) were coated with the recombinant or HSV antigens diluted in carbonate buffer overnight at 4°C. The supernatants of COS7 cells transfected with pBgDdTM or pcDNA3.1(−) were diluted 1:500 and were used as the coating antigen. Ten nanograms per well of the gG-1 or gG-2 antigen was used for the recombinant antigen-based ELISA, whereas 100 ng per well of HSV-1 or HSV-2 antigens was used for the whole-virus antigen-based ELISA. The prepared plates were blocked with blocking buffer (phosphate-buffered saline [PBS] containing 3% bovine serum albumin) for 2 h at room temperature. After each incubation step, the plates were washed three times with PBS containing 1% Tween 20 (PBST) and four times before the enzyme-substrate reaction step. The serum samples were serially diluted fourfold from 1:100 to 1:25,600 with dilution buffer (PBST containing 1% bovine serum albumin). One hundred microliters of the diluted serum was added to each well, and the plate was incubated for 2 h on a plate shaker at room temperature. Biotin-conjugated secondary antibodies were used in the present study. Donkey anti-rabbit immunoglobulin G (IgG; Chemicon International Inc.) diluted 1:100,000 in the dilution buffer, goat anti-monkey IgG γ chain (Rockland Immunochemicals Inc.) diluted to a concentration of 25 ng/ml, and goat anti-human IgG (Fc) (American Qualex International Inc., CA) diluted to a concentration of 6.25 ng/ml were used for the detection of rabbit, monkey, and human IgG, respectively. The secondary antibody reaction step was performed for 1 h on the plate shaker at room temperature. Streptavidin-conjugated β-galactosidase was diluted at 1:1,000 in the dilution buffer, and 100 μl was added to each well. The reaction was performed for 1 h on the plate shaker at room temperature. The enzyme-substrate reaction with a 0.2 mM 4-methylumbelliferyl-β-D-galactoside substrate solution was performed for 2 h at 37°C and was stopped by adding 0.1 M glycine (pH 10.3). The amount of fluorescent reactant was calculated as the number of fluorescence units (FUs) after measurement of the absorbance at 460 nm with a fluorometric microplate reader (Fluoroskan II; Labsystems, Tokyo, Japan). The FU values for the positive antigens subtracted from those for the negative antigens were used to evaluate the reaction in the ELISA. Reactions with values of less than 500 were considered negative. Antibody titers were taken as the reciprocal of the final dilutions on titration curves which gave positive reactions.

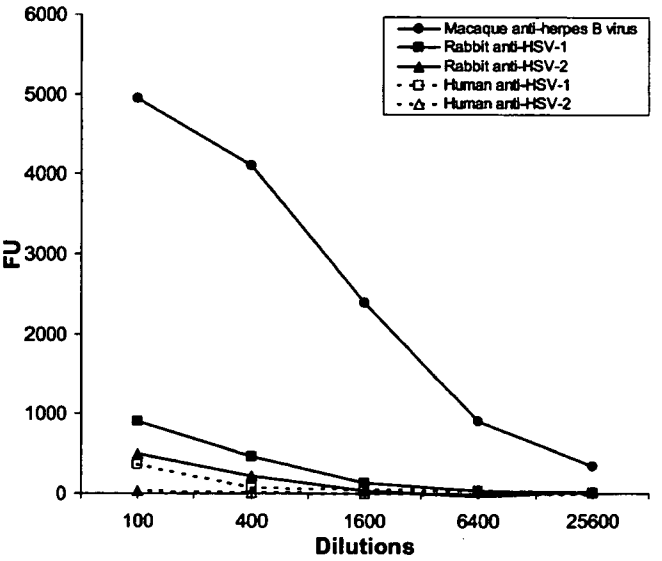

FIG. 1. Reactivity of the control sera with the herpes B virus gDdTM antigen. The results obtained with rhesus macaque serum which contained antibody to herpes B virus, rabbit sera immunized with HSV-1 or HSV-2, and human serum which contained antibody to HSV-1 or HSV-2 are shown. Sera were serially diluted fourfold from 1:100 to 1:25,600, and the FU values for each dilution were obtained by the fluorometric indirect ELISA with herpes B virus gDdTM. The FU values were plotted against each dilution of serum. The resulting titration curves are shown.

RESULTS

Antigenic specificity of recombinant herpes B virus gD. The reactivities of control sera for herpes B virus, HSV-1, or HSV-2 against the secretory form of herpes B virus gD lacking TM and CT (gDdTM) were investigated. Serum collected from rhesus macaques naturally infected with herpes B virus showed high levels of reactivity to the recombinant antigen (Fig. 1). The FU values for serial dilutions of the serum samples were almost linear, suggesting that specific binding between the coated antigen and the antibody in the serum occurred. The titer was 6,400. Sera from an uninfected macaque, rabbit, and human had low FU values (less than 500), suggesting no reactivity to the positive antigen (data not shown). Although the serum sample from a rabbit immunized with HSV-1 showed a

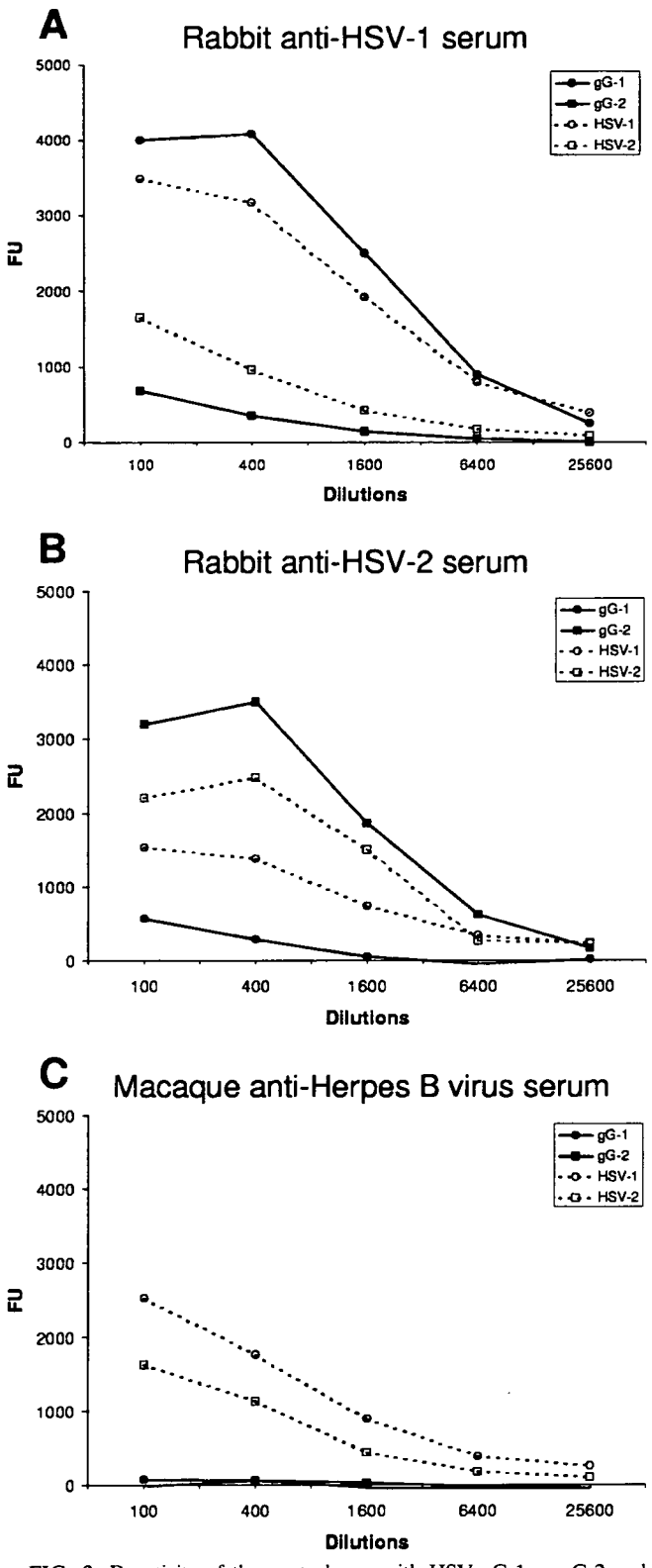

FIG. 2. Reactivity of the control sera with HSV gG-1 or gG-2 and whole-virus (HSV-1 or HSV-2) antigens. The results for rabbit anti-HSV-1 sera (A), rabbit anti-HSV-2 sera (B), and rhesus macaque anti-herpes B virus sera (C) are shown. The titration curves were obtained as described in the legend to Fig. 1, except that gG or HSV was used as the coating antigen. In each panel, four titration curves show the reactivity of the serum with the gG-1, gG-2, HSV-1, and HSV-2 antigens.

TABLE 1. Titers of antibodies to recombinant or whole primate herpesvirus antigens in rhesus macaque sera

Monkey no.	Antibody titer[a]				
	Anti-gD	Anti-gG-1	Anti-gG-2	Anti-HSV-1	Anti-HSV-2
7	UD	UD	UD	UD	UD
8	UD	UD	UD	UD	UD
9	UD	UD	UD	UD	UD
10	UD	UD	UD	UD	UD
11	UD	UD	UD	UD	UD
1308	200	UD	UD	200	UD
1309	UD	UD	UD	UD	UD
1333	3,200	UD	UD	800	UD
1371	3,200	UD	UD	UD	UD
1373	800	UD	UD	800	UD
1376	UD	UD	UD	UD	UD
1379	3,200	UD	UD	400	UD
1381	ND[a]	ND	ND	ND	ND
1383	UD	UD	UD	UD	UD
1385	UD	UD	UD	UD	UD
1386	3,200	UD	UD	3,200	800
1395	UD	UD	UD	UD	UD
1401	6,400	1,600	UD	3,200	800
1402	1,600	UD	UD	1,600	400
1403	1,600	UD	UD	1,600	UD
1404	UD	UD	UD	UD	UD
1413	3,200	UD	UD	3,200	200
1416	1,600	UD	UD	1,600	400
1417	800	UD	UD	800	UD

[a] Abbreviations: UD, under the detection limit (titer, <100); ND, not determined.

slight cross-reaction with a titer of 100 (Fig. 1), the other HSV-1- or HSV-2-infected rabbit and human serum samples showed no reactivity to the antigen of herpes B virus.

Antigenic specificity of recombinant gG-1 and gG-2. Anti-herpes B virus macaque serum and anti-HSV-1 and anti-HSV-2 rabbit and human sera were investigated for their reactivities to gG-1 or gG-2 by the fluorometric indirect ELISA. The results were compared with those obtained by the ELISA with the HSV-1 or the HSV-2 antigen. Virus-uninfected macaque, rabbit, and human sera did not react with any recombinant or whole-virus antigen (data not shown). Sera from the rabbits infected with HSV-1 or HSV-2 reacted not only with the homologous antigens but also with the heterologous antigens in the gG- and HSV-based ELISAs (Fig. 2A and B). The antibody titers obtained under the homologous antigen-antibody conditions, however, were higher than those obtained under the heterologous antigen-antibody conditions. Under the homologous conditions, the titers obtained by the gG-based ELISA were higher than those obtained by the HSV-based ELISA, while under the heterologous conditions, the titers showing the reaction to gG were lower than those showing the reactions to the virus antigens. In addition, the human control serum for HSV-1 reacted only with the homologous antigens, and the reactivity to gG-1 was higher than that to the HSV-1 antigen (data not shown). The human control serum for HSV-2 showed a notably higher reaction to gG-2 than to any of the other antigens tested (data not shown). A macaque anti-herpes B virus serum was found to cross-react with the whole-virus antigens but not with gG (Fig. 2C).

Application to rhesus macaque sera. Twenty-four serum samples from rhesus macaques in a laboratory facility were

TABLE 2. Titers of antibodies to herpes B virus, HSV-1, and HSV-2 in humans with no clinical symptoms

Control subject no.	Antibody titer				
	Anti-gD	Anti-gG-1	Anti-gG-2	Anti-HSV-1	Anti-HSV-2
1	UD[a]	3,200	UD	3,200	UD
2	UD	6,400	UD	3,200	200
3	UD	UD	UD	UD	UD
4	UD	UD	UD	UD	UD
5	UD	UD	UD	UD	UD
6	UD	800	800	400	UD
7	UD	3,200	UD	3,200	200
8	UD	3,200	UD	3,200	200
9	UD	3,200	UD	3,200	UD
10	UD	UD	UD	UD	UD
11	UD	UD	UD	UD	UD
12	UD	6,400	UD	3,200	400
13	UD	UD	UD	UD	UD
14	UD	UD	UD	UD	UD
15	UD	UD	UD	UD	UD
16	UD	UD	UD	UD	UD
17	UD	UD	UD	UD	UD
18	UD	UD	UD	UD	UD
19	UD	UD	UD	UD	UD
20	UD	6,400	UD	6,400	400
21	UD	3,200	UD	6,400	400

[a] UD, under the detection limit (<100).

examined for the presence of antibodies to the five antigens gDdTM, gG-1, gG-2, HSV-1, and HSV-2. The antibody titers were calculated for each antigen (Table 1). Twelve of the 24 macaque serum samples were found to have antibody to the herpes B virus gD. Among these 12 serum samples, 1 showed reactivity to the gG-1 antigen and none showed reactivity to the gG-2 antigens, whereas 11 had antibodies to HSV-1 and 5 had antibodies to HSV-2. The titer of antibody to HSV-1 was higher than that to HSV-2 in five serum samples (serum samples 1386, 1401, 1402, 1413, and 1416) in which antibodies to both HSV-1 and HSV-2 were detected.

Assessment of human control and patient sera. Twenty-one serum samples collected from human controls were investigated for antibodies to the five antigens (Table 2). None of the serum samples had antibody to gDdTM. Of the 21 serum samples, 9 were found to have antibody to gG-1 and 1 was found to have antibody to gG-2. The results obtained by the ELISA with gG-1 were identical to those obtained by the ELISA with HSV-1, whereas the results of the ELISAs with gG-2 and HSV-2 were not identical.

Five serum samples from patients diagnosed with central nervous system HSV infections were examined for the presence of antibodies to the five antigens (Table 3). None of the serum samples had antibody to gDdTM. The results obtained by the gG-based ELISA developed in the present study were the same as those obtained by the previous ELISA (17): two serum samples (serum samples P-1 and P-4) had antibodies to both gG-1 and gG-2, two (serum samples P-2 and P-3) had only anti-HSV-2 antibody, and the fifth (serum sample P-5) did not have antibody to either gG-1 or gG-2. However, three serum samples (serum samples P-1, P-2, and P-4) showed reactivity to both HSV antigens, whereas the other two serum samples did not react with any viral antigens.

DISCUSSION

Sensitive reactions to recombinant antigen gDdTM, gG-1, and gG-2 were shown by the control sera from rhesus macaques, rabbits, and humans. Although a slight cross-reaction was observed, the ELISA with the recombinant antigens was confirmed to show specificity for the detection of herpes B virus and HSV infections. The specificity of herpes B virus gD was also demonstrated, and it is proposed that gD may be a valuable diagnostic reagent for the identification of herpes B virus infections (19, 20). In our study, all macaque sera except the serum from one individual that reacted to the HSV antigen were also confirmed to have antibody to gDdTM but not to gG. In contrast, all human control and patient serum samples positive for the whole-virus antigen had antibody to gG-1 and/or gG-2 but did not have antibody to gDdTM. The limited detection of antibody to the recombinant proteins in the only natural hosts supports the specificity of the recombinant antigen-based ELISA. Taken together, we suggest that use of the combination of the recombinant proteins from herpes B virus and HSV is suitable for the discrimination of herpes B virus infection from HSV infection.

The herpes B virus recombinant antigen, gDdTM, does not contain the TM and CT regions, in which a linear B-cell epitope spanning residues 362 to 370 was found (19). In our previous study, we found that some serum samples seropositive for herpes B virus failed to react to gDdTM by WB analysis but could be found to have antibody to this secretory form of the protein by dot blot analysis (24). In accordance with our findings, the recombinant gD lacking the linear epitope was found to have a reduced reactivity to anti-herpes B virus serum under denatured conditions, suggesting the presence of conforma-

TABLE 3. Titers of antibodies to recombinant or whole primate herpesvirus antigens in patient sera

Patient no.	Diagnosis	Virus(es) detected by[a]:		Antibody titer				
		PCR	ELISA	Anti-gD	Anti-gG-1	Anti-gG-2	Anti-HSV-1	Anti-HSV-2
P-1	Myelitis	HSV-2	HSV-1 and HSV-2	UD[b]	3,200	3,200	200	200
P-2	Meningitis	HSV[c]	HSV-2	UD	UD	800	400	400
P-3	Meningitis	ND[d]	HSV-2	UD	UD	800	UD	UD
P-4	Meningitis	ND	HSV-1 and HSV-2	UD	800	400	3,200	200
P-5	Meningitis	HSV-1	ND	UD	UD	UD	UD	UD

[a] DNA and detection of antibodies to HSV-1 and HSV-2 were performed by PCR and a gG-based ELISA, respectively, in a previous study (19).
[b] UD, under the detection limit (<100).
[c] DNA was amplified from the cerebrospinal fluid of patient P-2, but the type could not be determined (17).
[d] ND, not detected.

tion-dependent epitopes in the extracellular domain (19). In the present study, gDdTM was used under nondenatured ELISA conditions. The results showed that an anti-herpes B virus macaque serum reacted strongly with the secreted form of herpes B virus gD, whereas a negative serum did not. In addition, the investigation of rhesus macaque sera showed that the gD-based ELISA did not fail to detect antibody in any serum sample which cross-reacted with the HSV antigens. Thus, it is suggested that the ELISA developed is able to detect antibodies by recognizing the epitopes in the extracellular domain.

Although we did not compare the sensitivity and specificity of the recombinant gD antigen with those of the whole herpes B virus antigens, the gG antigen was evaluated by comparison with the HSV antigen in experiments with anti-HSV-1 and anti-HSV-2 sera. The titers obtained by the gG-based ELISA were higher than those obtained by the HSV-based ELISA under the homogeneous antigen-antibody conditions, suggesting that the sensitivities of the recombinant proteins were higher than those of the whole-virus antigens. In contrast to this finding, the titers obtained by the recombinant antigen-based ELISA were lower than those obtained by the whole-virus-antigen-based ELISA under the cross-reactive conditions between HSV-1 and HSV-2, suggesting that the specificity for the recombinant antigens was greater than that for the whole-virus antigens.

A sample of macaque serum (serum sample 1401) was found to have antibody not only to gG-1 but also to herpes B virus gD. The other macaque serum sample with herpes B virus infection, however, did not have antibody to either gG-1 or gG-2. These results suggest a specific reaction of the serum sample (serum sample 1401) to gG-1. We concluded that this macaque had multiple virus infections (i.e., it was infected with HSV-1 as well as herpes B virus), although we could not determine which virus affected this individual first. The macaques investigated had opportunities to be exposed to HSV-1 and HSV-2 from laboratory workers. However, no animals had antibody to gG-2. Macaques in laboratory facilities might have more frequent opportunities to be exposed to HSV-1 than to HSV-2 because of the higher prevalence of HSV-1 infection in humans (3, 5, 28, 29).

We examined the existence of antibodies to the recombinant herpes B virus or HSV proteins in sera from patients diagnosed with HSV meningitis or myelitis, since the clinical symptoms caused by HSV infections are almost the same as those caused by herpes B virus infection. We did not detect antibody to gDdTM in these samples, whereas most of the patients were found to have antibody to gG-1 and/or gG-2. Although we could not examine serum from patients with herpes B virus infections, the identification of multiple infections in a macaque serum sample suggests that the ELISA developed can detect antibody to herpes B virus even in patients who have already been infected with HSV. On the other hand, serum taken from one patient (patient P-5) was not found to contain antibody to gG-1 or gG-2, even though HSV-1 DNA was amplified from the patient's cerebrospinal fluid. No antibody to gG was detected in the serum of this patient in the previous study either (17). In addition, this serum sample was also found not to have antibody to either HSV-1 or HSV-2. Therefore, it appears that this patient did not produce IgG antibody in the serum. Further investigation, such as tests for the detection of IgM antibody, would be required.

Eleven of 12 macaque serum samples confirmed to have antibody to herpes B virus were found to show cross-reactivity with HSV-1, whereas only 5 showed cross-reactivity with HSV-2. In addition, in all HSV-1- and HSV-2-seropositive macaques, the titers of antibodies to HSV-1 were higher than those to HSV-2. These results suggest that herpes B virus has more antigenic cross-reactivity with HSV-1 than with HSV-2. This suggestion could be supported by the findings in a report by Eberle et al. (6), in which the cross-neutralization titers of anti-herpes B virus serum to HSV-1 were shown to be higher than those to HSV-2. Complete genomic sequence analysis of herpes B virus showed that there are 20 proteins which are more similar to HSV-1 proteins, including capsid proteins, whereas another 46 proteins are more similar to HSV-2 proteins and include DNA cleavage and packaging proteins (21). Therefore, the higher degrees of similarity of the structural proteins recognized by the humoral immune system might explain the higher cross-reactivity of herpes B virus with HSV-1 than with HSV-2. However, gD and gG are not likely to contribute to the cross-reaction between herpes B virus and HSV.

In summary, the fluorometric indirect ELISA with recombinant herpes B virus gD and HSV gG was shown to have the potential to discriminate between herpes B virus infection and HSV-1 and HSV-2 infections in humans and macaques. In addition to the clinical aspect, this ELISA would contribute to the assessment of the seroprevalence of alphaherpesvirus infections in humans and primates, including the natural hosts of herpes B virus.

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INTERNAL MEDICINE

ORIGINAL ARTICLE

Longitudinal Analysis of Cytokines and Chemokines in the Cerebrospinal Fluid of a Patient with Neuro-Sweet Disease Presenting with Recurrent Encephalomeningitis

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Abstract

Background Neuro-Sweet disease (NSD) has recently been identified as Sweet disease with central nervous system (CNS) involvement characterized by multisystem neutrophilic infiltration. However, the pathogenesis of this disease remains unknown. Neutrophil and other inflammatory cell activities are influenced by many cytokines and chemokines, but to date, no studies have examined the levels of these factors in patients with NSD.

Patient and Methods The patient presented with encephalomeningitis twice in one year and was diagnosed with NSD. We measured the levels of cytokines (i.e., IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α) and chemokines (i.e., CCL2, CCL3, CCL5, CXCL8, CXCL10 and GM-CSF) in 10 CSF samples from the patient longitudinally for one year including those during two episodes of encephalomeningitis.

Results The elevations of IL-6, IFN-γ, CXCL8 (IL8) and CXCL10 (IP10) were markedly higher than the levels in uninfected control subjects with neurological disorders. The levels of these cytokines and chemokines were statistically correlated with total CSF cell counts ($p < 0.01$).

Conclusion CD4+ helper T (Th) cells can be divided into the Th1 and Th2 subtypes according to their cytokine secretion patterns, and IFN-γ and IP10 are the Th1-type cytokine and chemokine indicating the involvement of Th1 cells in NSD. In addition, the level of IL8, a specific neutrophil chemoattractant, correlated well with the neutrophil cell counts in CSF. Our data suggest the important roles of Th1 cells and IL8 in the pathogenesis of NSD.

Key words: CXCL8 (IL-8), CXCL10 (IP-10), IL-6, IFN-γ, neutrophil cell, Th1 cell

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Introduction

Neuro-Sweet disease (NSD) has recently been identified as Sweet disease with central nervous system (CNS) involvement characterized by multisystem neutrophilic infiltration (1, 2). Patients present with painful erythematous plaques on their skin and histological examination of the plaques shows dense dermal infiltration of neutrophils with no signs of vasculitis. This characteristic finding, together with HLA B51 negativity, is important in distinguishing NSD from neuro-Behçet disease (NBD) (2, 3). Japanese patients with NSD also typically show high levels of HLAs B 54 and CW1 (2).

Encephalitis and meningitis are common neurological manifestations of NSD (1). Systemic corticosteroid therapy is highly effective and most patients recover from their neurological deficits without sequelae (1, 2, 4, 5). Despite effective treatment, however, some patients have recurrent episodes indicating that more effective therapies are still needed. A clearly defined pathogenesis for NSD and reliable laboratory markers reflecting disease activity remain elusive. Here, we report the first longitudinal analysis of the levels of cytokines and chemokines in the cerebrospinal fluid

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