表 2　慢性進行型神経Behçet病の臨床像[3]

patients	CNS manifestations	finding on MRI scans
58 F	dementia, ataxia, dysarthria	scattered T2 high, Bs atrophy
68 M	dementia, ataxia, dysarthria	scattered T2 high, Bs atrophy
28 M	dementia, ataxia, dysarthria	Bs atrophy
35 M	psychosis	unremarkable
45 F	dementia, myclonus, ataxia, dysarthria	Cbr & Bs atrophy
48 M	dementia, ataxia, dysarthria	scattered T2 high, Bs atrophy
59 M	psychosis, ataxia	scattered T2 high, Bs atrophy
53 M	dementia, ataxia, dysarthria	scattered T2 high, Cbr & Bs atrophy
50 M	dementia, ataxia, dysarthria	Bs atrophy
53 M	dementia, ataxia, dysarthria	Cbr & Bs atrophy
37 M	dementia, ataxia, dysarthria	Cbr & Bs atrophy

Bs：brain stem, Cbr：cerebrum.

表 3　慢性進行型神経Behçet病11例のまとめ

clinical findings	
dementia/psychosis	11
ataxia	10
dysarthria	9
myoclonus	1
MRI findings	
atrophy	
brianstem/cerebellum	10
cerebrum	4
sccattered T2 high lesions	5

行し，ついには廃人同様になってしまう一群が存在することが強く認識されてきた[2]．こうした病型は急性型 NB に比べ，治療反応性と予後がまったく異なることから，近年，慢性進行型 NB とよばれて区別されるようになった[3]．自験 11 例ではその臨床症状として精神症状(痴呆・人格変化)，ataxia，構語障害がそれぞれ 11 例，10 例，9 例にみられ，頻度が高かった(表 3)．これに一致して，MRI では脳幹・小脳の atrophy が 10 例に，また大脳の atrophy が 4 例に認められた(図 2)．T2 強調画像での散在性の小さな high intensity lesion は 5 例に認められたが，かならずしも慢性進行型 NB に特異的な変化ではなく，むしろこれらの変化は神経症状のない Behçet 病患者にも散見される．

慢性進行型 NB の臨床的特徴は，急性型 NB に起因する脳局所徴候が先行症状として一過性に出現した後に，数年の間をおいて痴呆・精神症状や構語障害，ataxia が出現し，これが徐々に進行し，ついには患者は廃人同様となってしまうという点である[9]．患者の性別では男性に圧倒的に多く，HLA-B51 の Behçet 病全体での陽性率はたかだか約 50%強であるが，慢性進行型 NB においては自験 11 例中 9 例が HLA-B51 陽性であった[3]．一方，髄液中の細胞数・蛋白はごく軽度上昇するかあるいは正常であるにもかかわらず，髄液 IL-6 活性が数カ月以上持続して異常高値を示すことが明らかになっている[9]．これに対して，急性型 NB では症状の軽快とともに髄液 IL-6 活性は細胞数，蛋白と平行して低下する．一般的には慢性進行型 NB では髄液 IL-6 が 0.1 U/ml(20 pg/ml)以上で長期間存続する[9]．髄液 IL-6 値は細胞数，総蛋白，Q アルブミン値，血清 IL-6 のいずれとも有意の相関を示さず，中枢神経内で産生されていると考えられる[9]．

慢性進行型 NB は副腎皮質ステロイドやシクロホスファミドなどでは寛解導入することは困難である．副腎皮質ステロイドを大量に使用して髄液所見が軽快しても，減量に伴ってかならず再発がみられることから，プレドニゾロン 10 mg/day 以上は使用するべきではない．

著者らは近年，メトトレキサートの少量パルス療法により髄液中 IL-6 が劇的に低下した症例を経験した．そこで，このメトトレキサートの少量パルス療法の慢性進行型 NB に対する有用性を検討するためにオープン試験を行った[10]．その結果，メトトレキサート開始後(7.5～15 mg/wk)12 カ月において投与前に比べ髄液 IL-6 は有意に低下し，症状の進行も認められなかった．副作用としては肝障害を示した例が数例みられたが，メトトレキサートの減量でいずれも軽快した．肝障害はメト

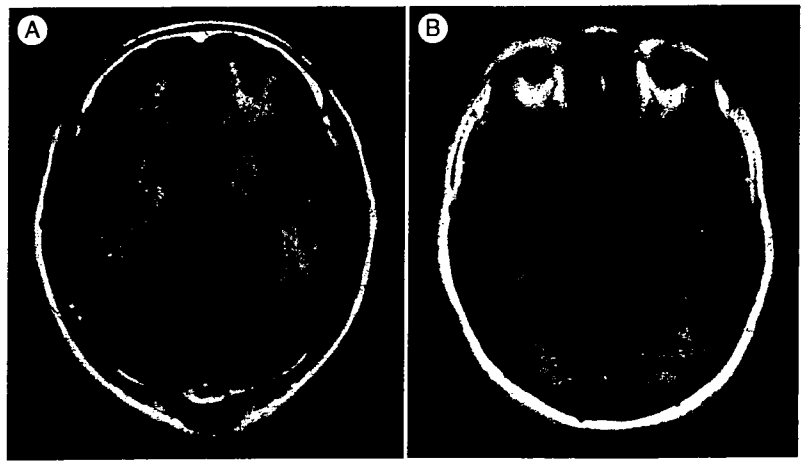

図 2　慢性進行型神経Behçet病患者のMRI所見(フレア画像)
A：大脳の萎縮，B：脳幹小脳の萎縮.

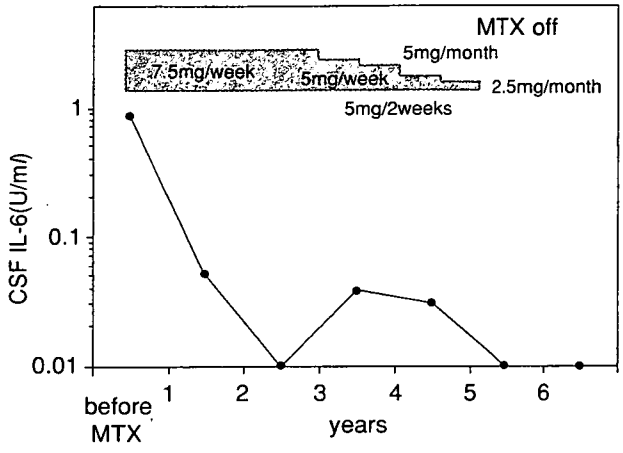

図 3　慢性進行型神経Behçet病でメトトレキサートを中止しえた代表例

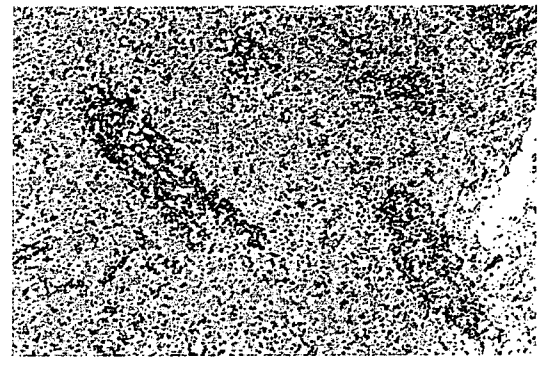

図 4　神経Behçet病患者の脳組織所見(H & E 染色，原倍率×25)

トレキサートによる葉酸代謝阻害に基づくことが知られており，最近はメトトレキサート内服 24〜48 時間に folate 5 mg を内服させるよう推奨されている．投与開始 12 カ月後でメトトレキサートを中止した場合，その 6 カ月後にはほとんどの例で髄液 IL-6 の上昇とともに症状の再燃がみられたため，メトトレキサートを再開するに至っている[10]．その後，髄液 IL-6 が低値のまま 2 年間以上持続した後に，髄液 IL-6 の値をみながらメトトレキサートを徐々に減量し，中止しえた症例を 2 例経験するに至っている(図 3)[11]．この 2 例についてはメトトレキサート中止後 6 カ月以上経ても髄液 IL-6 の上昇はなく，症状の増悪もみられていない．したがって，メトトレキサート少量パルス療法は慢性進行型 NB の寛解導入療法として十分期待がもてる治療法であると考えられる．

NBの病理学的特徴

NB においては，大脳，脳幹，小脳に特徴のある病理学的変化が認められる．その病理学的特徴は，図 4 に示すような毛細血管や細静脈周囲を中心とした脳実質への単核球，多核白血球の浸潤像が脳幹・大脳基底核・大脳白質にわたって多発性に認められる点である．脳実質に浸潤しているのは主として T リンパ球である．また，これらの炎症巣およびその周囲においては神経細胞のアポトーシスも認められる(図 5)[12]．さらに，活動性の NB で死亡した患者の脳においてしばしば 2 核のニューロンがみられる[13]．このような 2 核のニューロンがいかなる機序で出現するのかは不明であるが，IL-6 などにより生じたニューロンの変性やアポトーシスなどが原因として考えられる．

今後の問題点

慢性進行型 NB の病態を解明することは，

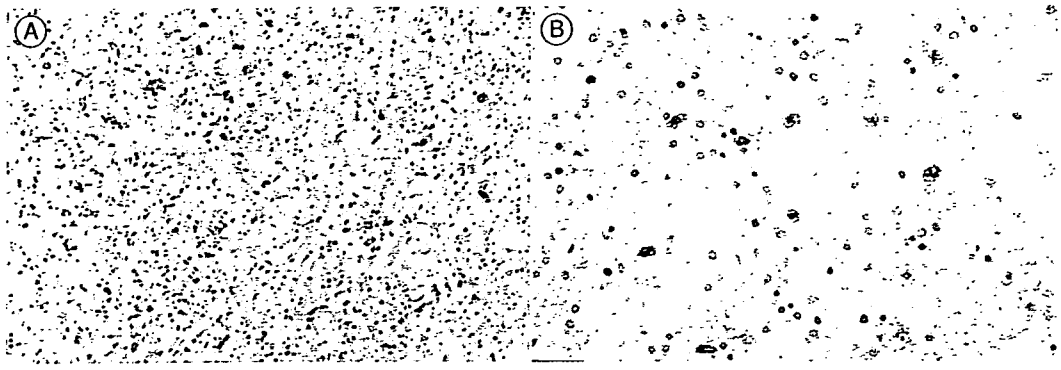

図 5　神経Behçet病患者の脳組織にみられた神経細胞のアポトーシス(原倍率×25)
右側の Tunnel 染色でアポトーシスを起こした神経細胞が陽性に染まっている.

Behçet 病のなかでこの病態を示す患者の予後がもっとも悪いことからきわめて重要である. メトトレキサートが髄液 IL-6 を低下させ症状の進行を食い止める効果を有することが明らかになったが, 今後はメトトレキサートの作用機序とともに髄液の IL-6 の持続性の上昇がいかなる機序で起こるかについて解明していく必要がある. また, メトトレキサートで効果不十分な症例についての対策も考えていく必要があろう(「サイドメモ」参照). さらに, 急性型 NB から慢性進行型に移行するポイントをいかにして同定するか, また HLA-B51 がいかに病態形成に関与するかについても明らかにしていかなくてはならない.

サイドメモ

関節リウマチと慢性進行型神経 Behçet

関節リウマチ(RA)と慢性進行型神経 Behçet(NB)の2つの疾患は一見何の関係もないようにみえる. しかし, この2つには意外に共通点が多いのである. まず, 両者ともに発症に遺伝的素因が関与している点である. RA は HLA-DR4, 慢性進行型 NB は HLA-B51 と強い相関がみられる. また, RA も慢性進行型 NB も副腎皮質ステロイドのみでは寛解導入できず, メトトレキサート少量パルス療法が有効である点, さらに両者とも徐々に進行して組織破壊をきたす点も共通している. また, 炎症局所において IL-6 が高濃度に存在することも共通している. 近年, RA の治療において抗 TNF-α 抗体療法(infliximab)の有効性が強く認識されている. Behçet 病の眼病変に対しても infliximab が有効であることが証明されている. はたして, infliximab の慢性進行型 NB に対する効果はどうであろうか.

一方, 急性型 NB において, とくにシクロスポリン A が中枢神経病変を誘発する機序を明らかにすることは, NB そのものの発症機序を解明する重要な糸口になると思われる.

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Clin Rheumatol, 17: 278～282, 2005

中枢神経病変

Key words: neuropsychiatric lupus erythematosus, steroid psychosis, cerebrospinal fluid, IL-6, treatment

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はじめに

膠原病の中でも，特に全身性エリテマトーデス（SLE）においては，多彩な中枢神経病変を呈する[2]．これらの中枢神経病変は時として治療に難渋する場合が多く，いわゆる難治性病態の1つに掲げられている．アメリカリウマチ学会（ACR）は1999年にSLEの精神神経症状の新分類基準[1]を提唱し，中枢神経病変を，局所病変を主徴とするneurologic syndromesと高次脳機能異常を主徴とするdiffuse psychiatric/neuropsychological syndromesの2つに分類し，さらに後者を5つの症状に分類している．表1に示すように，従来organic brain syndromeと呼ばれていたものはacute confusional stateの一部とcognitive disorderに相当すると考えられる[2]．本稿においては，こうしたSLEに見られる高次脳機能異常の治療について，これまでの自験例を提示しながら考えてみたい．

1．SLEに起因する精神症状（diffuse psychiatric/neuropsychological syndromes（ループス精神病）の診断

SLEの患者に精神症状が出現した場合．それがSLEに起因するもの（ループス精神病）であるかを診断するのは困難なことが多い．特に，副腎皮質ステロイドの開始後に精神症状が顕在化した場合，副腎皮質ステロイドの副作用（steroid psychosis）との鑑別が問題となる．さらに，ループス精神病とsteroid psychosisの両者が合併することも少なくないことが問題を一層複雑にしている[4]．これまでループス精神病においては髄液IL-6やIgG indexの上昇することを我々は報告してきた[3)5)]．平成14年度～16年度の厚生労働科学免疫アレルギー疾患予防・治療研究事業「免疫疾患の合併症とその治療法に関する研究」班において多施設共同研究を行い，転帰の明らかな過去10年間の81症例についてROC解析を行った結果，髄液IL-6値 4.3 pg/mlをカットオフ値とした場合，感度87.5%，特異度92.3%でループス精神病の診断ができるという結果を得た[6]．従って，現段階では，SLE患者に精神症状が出現した場合，髄液IL-6によりある程度確度を持って診断を下すこと

表1　ループス精神病の旧分類と新分類の対応

Organic brain syndrome
Acute confusional state
Cognitive disorder
Non-organic psychosis
Acute confusional state
Anxiety disorder
Mood disorder
Psychosis

Central nervous system involvement.

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ができるものと考えられる．但し，新たに発生した脳血管障害や感染性脳脊髄膜炎のある場合は，それだけで髄液 IL-6 は上昇するので，ループス精神病の診断マーカーとしては使用できない[6]．

2．ループス精神病の治療　—自験例のまとめ

表 2 に1983年～2003年までのループス精神病自験例20例のまとめを示す．精神症状としては acute confusional state を示すものが最も多く，また約半数の症例でけいれんを伴っていた．大半の症例は，副腎皮質ステロイド（パルスも含む）のみで治療され，免疫抑制剤を併用した症例は 4 例のみであった．全20例中 7 例が死亡している．

表 3 に死亡例の死因の内訳を示す．死亡例 7 例のうち原病のコントロール不全によるものは 3 例であり，このことより，大量の副腎皮質ステロイドと免疫抑制剤によってある程度の治療効果を上げることができると考えられる．治療の副作用によると考えられる死亡が 3 例あっ

表 2　ループス精神病：自験例のまとめ（1983～2003）

患者	男性 4 名　女性16名 37.7±14.4歳(Mean±SD)	
症状	Acute confusional state	11(8)*
	Acute confusional state ＋Cognitive disorder	1
	Cognitive disorder	3(1)
	Mood disorder	2
	Psychosis	3
治療内容	Steroid のみ（プレドニゾロン30～80 mg/日）	12例
	Steroid pulse 併用	8 例
	CPA or AZA 内服併用	2 例
	CPA pulse 併用	2 例
	Plasma exchange 併用	1 例
予後	20例中 7 例死亡（発症後 1 月～20年）	

＊（ ）内はけいれんを合併した例数
CPA＝cyclophosphamide，AZA＝azathioprine

表 3　ループス精神病：死因の内訳

1．原病のコントロール不全	3 例
尿崩症の合併	1 例
TTP の合併	1 例
脳出血（抗リン脂質抗体症候群にワーファリン併用）	1 例
Cyclophosphamide 内服継続による malignancy	1 例
急性心筋梗塞	1 例
3．その他の合併症	1 例
腸管のう気腫症によるイレウス	1 例

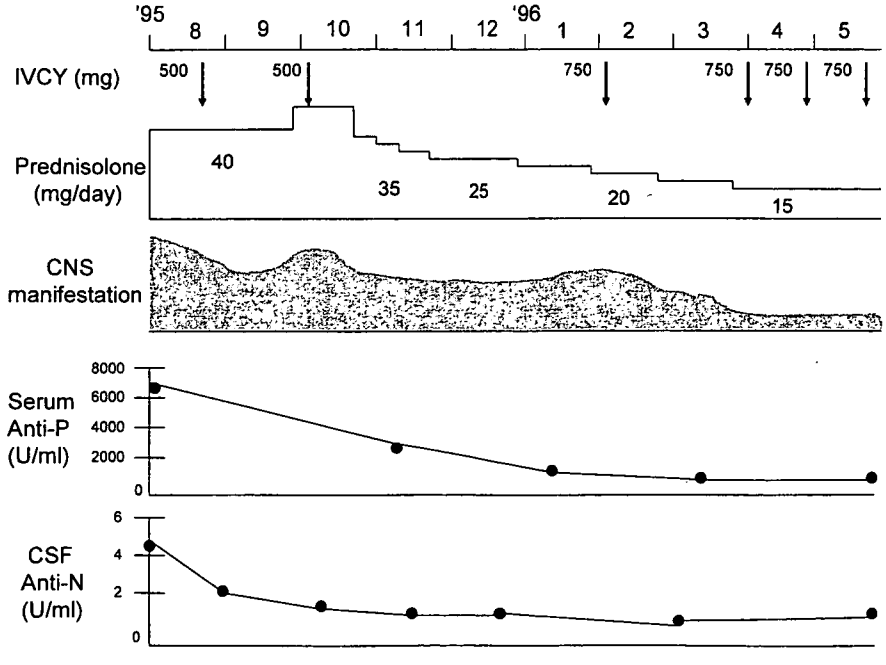

図 1　難治性のループス精神病の 1 例(1)

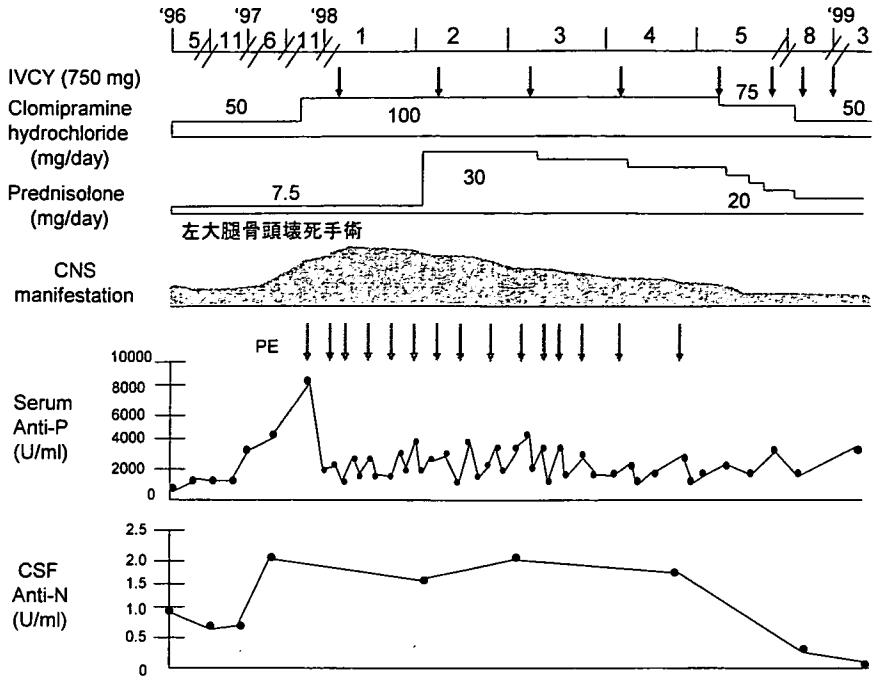

図2 難治性のループス精神病の1例(2)

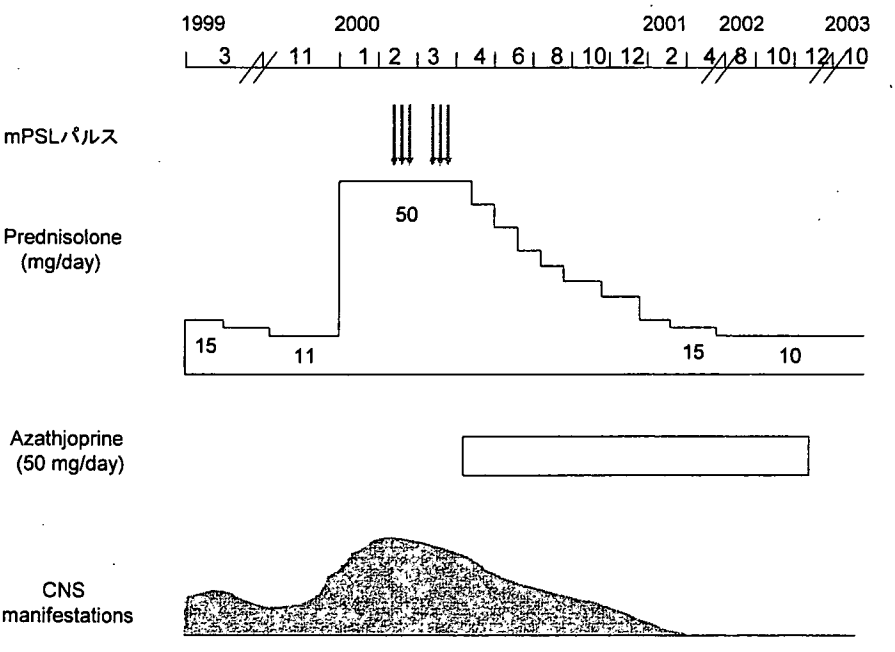

図3 難治性のループス精神病の1例(3)

た．このうちカリニ肺炎の1例はST合成による一次予防で発生は防げたと考えられる．また，シクロフォスファミド内服によるmalignancyの発生も，内服期間を一定期間以内（2年くらい）に限定することで予防可能と考えられる．急性心筋梗塞は，ループス精神病にかかわらず，SLEの治療一般における副腎皮質ステロイドによる動脈硬化予防という問題を提起するものである．総コレステロール値の上昇する例ではstatin系薬剤を投与すべきと考えられるが，evidenceを作ってゆく必要があろう．

図1～図3にシクロフォスファミドパルス療法と血漿交換療法を施行したループス精神病（mood disorder）の1症例の経過を示した．1995年8月～1996年5月までは内服プレドニゾロンとシクロフォスファミドパルス療法を施行しある程度軽快したが，コントロールは完全ではなかった(図1)．1996年5月大腿骨頭無腐性

壊死に対する左大腿骨頭置換術を契機に，血清抗リボソームP抗体，髄液抗神経細胞抗体の上昇とともに精神症状の増悪をきたした．血漿交換療法を繰り返し，シクロフォスファミドパルスを再開するも改善せず，結局副腎皮質ステロイドの増量によりデータの改善とともに症状も軽快し，塩酸クロミプラミン（抗うつ薬）の減量もできた(図2)．しかし，1999年11月に再発し，内服プレドニゾロンの増量とステロイドパルス療法に加え，アザチオプリン内服を2年間併用し，これによって寛解導入に成功し，以後約3年に亘って再発は見られていない（図3）．本症例からは，難治性のループス精神病に対しては，少なくとも十分量の副腎皮質ステロイドを使用した上で，アザチオプリン内服を行うことが，シクロフォスファミドパルス療法や血漿交換療法よりも有効であることが示唆される．

これまでSLEによる精神神経病変の治療として色々な方法が報告されている．表4に平成14年度～16年度厚生労働科学免疫アレルギー疾患予防・治療研究事業「全身性自己免疫疾患における難治背病態の診断と治療法に関する研究」班において作成したガイドラインを示す[7]．

表4　CNSループスの治療ガイドライン

治療法	神経症状 精神症状	横断性脊髄炎	その他
Steroid内服	A	A	B
Steroid pulse	B	B	B
Cyclophosphamide pulse	B		B
Steroid pulse +cyclophosphamide pulse		B	
免疫抑制剤内服	B		
血漿交換療法	C	C	
Steroid+methotrexateの髄腔内投与	C	C	C
抗CD20抗体(Rituximab)	C	C	
自家骨髄幹細胞移植	C	C	

ガイドラインにおける推奨の強さの分類
推奨A　行うよう強く勧められる
推奨B　行うよう勧められる
推奨C　行うよう勧められるだけの根拠が明確でない
推奨D　行わないよう勧められる

ループス精神病の治療として最も効果の確実なものは副腎皮質ステロイドであり，一般的に大量のプレドニゾロン（1 mg/kg体重）を使用する．ステロイドパルス療法やシクロフォスファミドパルス療法の有効性を示す報告は多いが，コントロール試験でその有用性を証明したものは1つもない．近年，リツキシマブ(抗CD20モノクローナル抗体）の有効性を示す報告がなされており，今後の臨床応用が期待される[8]．

おわりに

以上，SLEに起因する精神症状の診断とその治療について，自験例をまじえて概説した．副腎皮質ステロイドと免疫抑制剤による治療で35％の死亡例が出ている．SLEの10年生存率が90％を越える現在，この数字は決して満足できるものではない．現在，SLEの治療としてリツキシマブが大きな注目を集めている．その効果だけでなく，副腎皮質ステロイドや免疫抑制剤に比して重篤な副作用の少ないことも大きな魅力である．今後，SLEの中枢神経病変に対してもリツキシマブの有用性を検討してゆくことが，この難治性病態の克服に向けて重要な課題であると考えられる．

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Accuracy of Anti–Ribosomal P Protein Antibody Testing for the Diagnosis of Neuropsychiatric Systemic Lupus Erythematosus

An International Meta-Analysis

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Objective. **To quantitatively evaluate the diagnostic accuracy of antibodies to ribosomal P proteins (anti-P) for neuropsychiatric systemic lupus erythematosus (NPSLE) in general, for psychosis, mood disorder, or both, and for other diffuse manifestations.**

Methods. **This international meta-analysis combined standardized data from 1,537 lupus patients contributed by 14 research teams. Weighted estimation of sensitivity and specificity with fixed-effects and random-effects models, as well as summary receiver operating characteristic (SROC) curve analysis, was used to summarize test performance. The robustness of the overall estimates was examined in sensitivity analyses that included additional studies published up to November 1, 2004 in the Medline, EMBase, and Cochrane databases.**

Results. **Combining the data from the 14 teams, the weighted sensitivity and specificity estimates for the diagnosis of NPSLE were 26% (95% confidence interval [95% CI] 15–42%) and 80% (95% CI 74–85%), respectively. For psychosis, mood disorder, or both, the sensitivity and specificity were 27% (95% CI 14–47%) and 80% (95% CI 74–85%), respectively. For other diffuse manifestations, the sensitivity was 24% (95% CI 12–42%), and the specificity was 80% (95% CI 73–85%). The proportion of patients with anti-P antibodies did not vary markedly across different presentations of NPSLE. Between-study heterogeneity was substantial, but the SROC curves were consistent with the weighted estimates. In further analyses that included another 24**

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published studies, only the sensitivity for psychosis and/or mood disorder was slightly improved, but it was still suboptimal (42% [95% CI 30–53%]); the specificity remained essentially the same (81% [95% CI 76–85%]).

Conclusion. **Anti-P antibody testing has limited diagnostic value for NPSLE, and it is not helpful in differentiating among various disease phenotypes.**

Neuropsychiatric manifestations occur in approximately one-half of patients with systemic lupus erythematosus (SLE) and may cause substantial impairment of quality of life as well as disability (1–3). Moreover, multiple neuropsychiatric events during the disease course are associated with adverse long-term prognosis (4,5) and may lead to death, with a mortality rate of 7–19% (2,5,6). Neuropsychiatric SLE (NPSLE) encompasses a multitude of symptoms involving the central, peripheral, and autonomic nervous systems as well as psychiatric disorders (7). Recently, an ad hoc committee of the American College of Rheumatology (ACR) proposed a standard nomenclature for 19 neuropsychiatric syndromes associated with SLE (7), yet NPSLE is difficult to diagnose and is challenging to treat. Secondary factors, such as drugs, metabolic abnormalities, or infections, can also cause neuropsychiatric disturbances in lupus patients (3,7). Manifestations reflecting diffuse cerebral involvement pose the foremost difficulty in differentiating their exact origin, since psychiatric disorders may merely be reactive psychological disturbances (2,3,7).

During the last 2 decades, several studies have explored the utility of antibodies to ribosomal P proteins (anti-P) in detecting NPSLE (6,8–35). These antibodies are directed toward 3 large-subunit ribosomal phosphoproteins, called P0 (38 kd), P1 (19 kd), and P2 (17 kd), which share a common linear determinant in the carboxyl-terminal 22–amino acid sequence (36). Early studies claimed that serum anti-P antibodies were highly accurate for the diagnosis of SLE-mediated psychosis and depression (9,26), but subsequent reports were less optimistic (11–13,18,20,25,27,31). Other studies expanded the spectrum of neuropsychiatric features that could be correlated with anti-P to include active disease, diffuse manifestations, or NPSLE overall (6,25,28,30), making even more unclear their clinical value for this entity. Methodologic shortcomings, including the criteria used to define NPSLE, the approaches adopted for detecting anti-P antibodies, and the small sample size of isolated studies, may have contributed to the uncertainty.

Because SLE is a relatively uncommon disease and NPSLE is even more uncommon, no single study can reliably assess the operating characteristics of anti-P antibodies. Yet, a rigorous appraisal of a diagnostic test may reduce the number of unwanted clinical consequences related to misleading estimates of the accuracy of that test. Ideally, one would like to assess the diagnostic accuracy of a test across a large study population and use similar, standardized, and reproducible methods. In the absence of a single very large study that could do this, an attractive alternative is to standardize data across existing cohorts of lupus patients. Therefore, the aim of this study was to evaluate the diagnostic performance of anti-P antibodies for NPSLE in general, for diffuse NPSLE manifestations, and for particular psychiatric syndromes (psychosis, mood disorder, or both) in the context of an international collaborative meta-analysis, with standardization of the data contributed by a large number of investigators.

PATIENTS AND METHODS

Eligibility criteria. The meta-analysis included lupus patients with and without NPSLE who had undergone serum anti-P antibody testing by immunoblotting, a standard enzyme-linked immunosorbent assay (ELISA), or both (37–39).

To ensure consistency, participating investigators were asked to comply with the following rules. Patients had to fulfill the ACR criteria for the classification of SLE (40) and had to be evaluated for the presence or absence of neuropsychiatric lupus syndromes according to the ACR nomenclature and case definitions (7). Patients with a neuropsychiatric syndrome during any time in the course of SLE were classified into 3 subgroups: those with psychosis, mood disorders, or both; those with other diffuse (2,6) manifestations (including acute confusional state, generalized seizures, cognitive dysfunction, anxiety disorder, and headache other than migraine or cluster headache), and those with focal (2,6) neurologic events (including cerebrovascular disease, partial seizures, migraine or cluster headache, myelopathy, demyelinating syndrome, movement disorder, aseptic meningitis, and syndromes of the peripheral nervous system) (7). When both diffuse and focal events occurred in the same patient, the designation was made according to the predominant manifestation. Severe, sustained, or progressive presentations requiring more-aggressive

treatment with cytotoxic immunosuppressive agents were considered to be predominant.

Collaborating investigators provided a clear description of the immunoassay(s) used for anti-P determination, with sufficient detail to permit replication (41). When both immunoblotting and ELISA had been used, data were reported separately for each method. Patients who had undergone testing for anti-P multiple times were considered to have this autoantibody specificity if at least 1 of the determinations yielded positive results. Investigators were also asked to specify whether immunoassays were performed without knowledge of the clinical condition of the patients and whether the diagnosis of NPSLE, as well as the assignment of neuropsychiatric syndromes, was accomplished without knowledge of the anti-P status of the participants.

Organization of the international database. Research teams who have previously published data on cohorts of SLE patients were invited to participate in this meta-analysis, provided that the study patients met the eligibility criteria defined above. Collaborating teams were identified through searches of the Medline, EMBase, and Cochrane databases conducted in January 2003, using combinations of index terms (systemic lupus erythematosus, rheumatic diseases, connective tissue disease, or autoimmune disease, as well as ribosomal, antiribosomal, anti-P, or antineuronal), cited references of eligible studies and review articles, abstracts of major rheumatology conferences, and consultation with experts in the field. We e-mailed invitations to investigators working on SLE. The meta-analysis was also announced at an autoimmune disease–related scientific meeting (42). Pertinent data were contributed on a standard reporting form. The database remained open until July 2004.

Research teams from 14 centers (8 European, 4 Asian, and 2 South American) agreed to participate. We accepted data that were already available as well as data that were prospectively generated specifically by some of the participating teams for the purposes of the collaborative project. The effort was coordinated by the Clinical and Molecular Epidemiology Unit of the Department of Hygiene and Epidemiology at the University of Ioannina School of Medicine. The coordinating center was responsible for giving instructions to participating investigators on how to standardize and summarize their individual-level databases. The contributed data sets were assessed for potential errors or inconsistencies and then assembled at the coordinating center, which was also responsible for conducting the analyses. Queries were clarified through communications with the participating investigators.

Data synthesis and statistical analysis. Measures of diagnostic performance included sensitivity and specificity of anti-P antibodies for various forms of NPSLE. The main analysis involved the following 4 comparisons: NPSLE overall and each subgroup of NPSLE (psychosis and/or mood disorder, other diffuse manifestations, and focal events) versus the non-NPSLE group; all diffuse manifestations versus focal events; and psychosis and/or mood disorder versus other diffuse manifestations. These analyses address the discriminatory ability of the test for NPSLE in general, for each disease subtype, and for different neuropsychiatric presentations. To further pursue the possibility that anti-P may be specifically associated with particular psychiatric disorders (8,9,16,22,26), we evaluated the diagnostic accuracy of anti-P antibody for patients with psychosis and/or mood disorder versus all other lupus patients.

Test performance was estimated separately from studies that used immunoblotting for the detection of anti-P antibodies and from studies that used ELISA. In the overall analysis, when both immunoblotting and ELISA data were available from the same study, the results from the ELISA were used for the calculations. Diagnostic accuracy was also evaluated for subgroups defined by race.

Summary estimates were obtained with 2 meta-analytic methods: weighted independent estimation of sensitivity and specificity, and summary receiver operating characteristic (SROC) curve analysis.

Sensitivity and specificity estimates for each comparison were independently combined across studies, using both fixed-effects (Mantel-Haenszel) and random-effects (DerSimonian-Laird) models (43,44). Fixed-effects models weigh each study by the inverse of its variance. Random-effects models also incorporate between-study variation. The random-effects approach tends to provide wider confidence intervals (CIs) and is preferable in the presence of between-study heterogeneity. Except where indicated otherwise, random-effects estimates are provided below. Between-study heterogeneity was examined with Fisher's exact test.

Because sensitivity and specificity are interdependent, independent weighting may sometimes underestimate both measures. Hence, we used SROC curve analysis to account for this mutual dependence (45,46). The method fits a curve describing the tradeoff between sensitivity and specificity across studies, with different characteristics and thresholds for an abnormal test result. The regression is calculated as follows: $D = \alpha + \beta S$, where D is the difference in the logits of the true-positive rate (sensitivity) and the false-positive rate (1 – specificity), and S is the sum of these logits. When β is not significantly different from 0, the SROC curve is symmetric around the diagonal that runs from the top left corner to the bottom right corner of the diagram. Conversely, when β is significantly different from 0, the SROC curve is not symmetric, and the overall diagnostic performance varies in different parts of the curve, with an uneven tradeoff between sensitivity and specificity across studies. This may indicate significant between-study variation in the selected test threshold, study population, or other parameters. SROC curves should not be extrapolated outside the range of observed values. Both nonweighted and weighted SROC curves were estimated (46,47); nonweighted curves consider all studies equally in the calculations, whereas weighted curves weigh each study by the variance of D.

Inclusion of other published data. Sensitivity analyses were conducted to examine whether the addition of further relevant published studies affected our summary estimates of the operating characteristics of anti-P antibodies. Only the following 2 comparisons were examined, since articles focused on these patient groups: the entire group of NPSLE

patients versus the non-NPSLE patient group, and patients with psychosis and/or mood disorder versus either the non-NPSLE patients or all other lupus patients. Finally, we evaluated the available data to compare active NPSLE versus non-NPSLE.

Eligible studies published in any language were retrieved during the stage of identification of pertinent articles and collaborating investigators, as described above. We updated the literature search of the 3 computerized databases in November 2004 to identify additional relevant studies published up to November 1, 2004. Meeting abstracts were not included because the results may not be final and may not have been subjected to formal peer review. Duplicate or overlapping data were counted only once. The inclusion criteria were similar to those of the collaborative meta-analysis, with no restriction on patient age or study location. Nevertheless, in these analyses, we did not use the stringent criteria regarding the method of antibody determination and classification of neuropsychiatric disease; studies were combined regardless of the assay used to detect anti-P antibodies and regardless of the criteria used to diagnose NPSLE.

Other sensitivity analyses. We also performed sensitivity analyses to assess the robustness of the quantitative estimates derived from the collaborative meta-analysis. These analyses were limited to studies that used the ACR criteria for NPSLE syndromes and limited to studies that specified blinding.

Software. Analyses were conducted with the use of the following software: SPSS, version 12.0 (SPSS, Chicago, IL), Meta-Test, version 0.6, New England Medical Center, Boston, MA, 1997 (Joseph Lau, Tufts–New England Medical Center, Boston, MA) and Meta-Analyst, version 0.991 (Joseph Lau, Boston, MA).

RESULTS

General characteristics. We sent inquiries to 104 investigators working on SLE. Of those 104 investigators, 65 did not reply, 18 did not have any data and could not produce such data for the project, and 4 declined to participate. Of the last group, 2 investigators had published studies that were included in the sensitivity analysis.

The collaborative meta-analysis considered 1,537 lupus patients from 14 teams of investigators. Of these, 1,295 patients underwent both anti-P antibody testing by immunoblotting or standard ELISA and evaluation for NPSLE according to the ACR case definitions. The median sample size per study was 91 patients (interquartile range [IQR] 48–162). Women accounted for 80–97% of each study population. Although more than one-half of the participants were of European descent, patients of other ancestries were also included (Table 1). The mean age of the patients at study entry ranged from 29.8 years to 41.6 years, and the median of the mean disease durations across study cohorts was 7.3 years (IQR 6.2–7.8).

Most studies used a solid-phase ELISA, with highly purified synthetic peptides of the carboxyl-terminal 22–amino acid sequence (n = 4), a multiple-antigen peptide format (n = 3), and purified native (n = 2) or recombinant (n = 3) proteins as coating antigen to detect anti-P antibodies. Seven studies designated a positive anti-P result as >2 SD (n = 1) or >3 SD (n = 6) above the mean value obtained in a normal population, whereas 5 studies reported results according to the suggested threshold for the commercial ELISA systems they used. Only 4 studies used Western blotting on cell extracts from various sources for the detection of this autoantibody specificity. A single study used a line immunoassay, which is an ELISA-based multianalyte assay (Table 1).

The median prevalence of anti-P antibodies was 18.2% (IQR 9.7–28.6%). These antibodies were more prevalent in lupus patients of Asian descent than among those of other racial ancestries. The study-specific frequencies of anti-P antibodies were 23.8–45.5% in 320 patients of Chinese, Japanese, Taiwanese, and Filipino ancestry and 6.4–25.4% in 1,212 patients of other ancestry.

Approximately one-third of the 1,537 lupus patients had NPSLE that manifested as syndromes described in the ACR case definitions (median prevalence 32% [IQR 12–42%]). In 1 study (Table 1), neuropsychiatric involvement was determined according to prespecified criteria other than the ACR case definitions. Eight research teams provided individual patient data; in these studies, 8% of patients had >1 neuropsychiatric disorder, but only 5% had both focal and diffuse presentations. The other 6 teams directly collected data on only the most prominent manifestation. More than one-half of the NPSLE patients presented with disorders reflecting diffuse cerebral involvement (median prevalence 54.5% [IQR 47.6–68.2%]). The median prevalence of psychosis, mood disorder, or both was 24.9% (IQR 17.1–38.4%). In most studies, NPSLE was diagnosed without knowledge of the anti-P antibody status, and test interpreters were blinded to the clinical condition of the patients (Table 1).

Diagnostic performance of anti-P antibody testing. Substantial heterogeneity was found in both the sensitivity and the specificity of anti-P antibody testing

Table 1. Characteristics of the studies and patient populations included in the collaborative meta-analysis*

Study ID	Investigator, country, year (ref.)	Study setting	No. of patients	% women	Ethnicity (%)†	Mean age, years	Mean disease duration, years	Anti-P antibody assay	Prevalence of NPSLE, %	NPSLE manifestation			Blinding‡
										Psychosis and/or mood disorder	Other diffuse manifestations	Focal events	
1	Doria A, Italy, 2004	University	101	88	Italian (98), African (2)	29.8	6.7	WB/ELISA	21	8	6	7	T, C
2	Morozzi G, Galeazzi M, Italy, 2004	University	20§	90	Italian (85), Chinese/Filipino (15)	35.7	7.6	ELISA	15	0	0	3	T, C
3	Afeltra A, Italy, 2004	University	43	88	Italian	41.6	8	ELISA	93	2	16	22	T, C
4	Mathieu A, Italy; Sanna G, UK, 2000 (24)	University	68¶	96	Italian	38.4	7.7	ELISA	49	7	9	17	T, C
5	Hoffman I, De Keyser F, Belgium, 2004 (14)	University	235#	88	Belgian, Dutch, Slovak, English	40	7.2	LIA	59	33	32	51	NS
6	Tzioufas A, Greece, 2000 (30)	University	185	96	Greek	34.7	4.3	ELISA	9	2	7	8	NS
7	Ambrozic A, Slovenia, 2003	University	150	91	Slovenian	38.1	7.8	WB	39	11	14	33	T, C
8	Inanc M, Turkey, 2004	University	218	89	Turkish	38.5	7.8	ELISA	23	20	5	26	T, C
9	Chang D-M, Taiwan, 2003	Community	80	91	Taiwanese	35	9.4	ELISA	6	1	3	1	NS
10	Mok CC, China, 2004	Community	33	97	Chinese	36.2	7	WB/ELISA	33	3	5	3	T, C
11	Hirohata S, Japan, 2003	University	50	80	Japanese	40.8	2.6	ELISA	32	5	7	4	T, C
12	Yoshio T, Japan, 2003 (35)	University	154**	90	Japanese	34.6	4.7	ELISA	40	14	24	24	T, C
13	Massardo L, Chile, 2002 (21)	University	141††	90	Chilean	33	7	WB/ELISA	9	5	1	6	T, C
14	Spindler AJ, Argentina, 2003	University	59	92	Argentinean	36	7.3	ELISA	44	11	4	11	T, C

* References and publication dates (when the contributed data were derived from published studies) are provided; otherwise, the year the data were collected and sent to the coordinating center are shown. See Patients and Methods for a full description of the 3 subgroups of neuropsychiatric systemic lupus erythematosus (NPSLE). Anti-P = anti–ribosomal P; WB = Western blotting; ELISA = enzyme-linked immunosorbent assay; LIA = line immunoassay.

† Percentages are given for studies that included patients of different ethnicities, when known.

‡ NPSLE was diagnosed without knowledge of the results of the anti-P antibody testing (T), and test interpreters were blinded to the clincial data (C). NS = not specified.

§ In this study, 3 patients had indeterminate results for anti-P antibodies and were not included in the quantitative synthesis.

¶ In this study, 5 patients who were not tested for anti-P antibodies were not included in the quantitative synthesis.

In this study, sufficient clinical information for NPSLE was available for 196 patients; the presence or absence of NPSLE was assessed using prespecified criteria other than the American College of Rheumatology case definitions (7); and data for disease duration were available for 197 patients.

** Only 44 patients were included in the published study.

†† In this study, 2 patients in addition to the ones listed under NPSLE manifestations had NPSLE, but the type of involvement was not known.

Table 2. Summary results of the collaborative meta-analysis*

Comparison	No. of studies	No. of subjects	Weighted sensitivity (95% CI)	Weighted specificity (95% CI)
NPSLE versus non-NPSLE	13	1,340	0.26 (0.15–0.42)	0.80 (0.74–0.85)
Psychosis and/or mood disorder versus non-NPSLE	12	1,024	0.27 (0.14–0.47)	0.80 (0.74–0.85)
Other diffuse neuropsychiatric manifestations versus non-NPSLE	12	1,034	0.24 (0.12–0.42)	0.80 (0.73–0.85)
Focal neurologic events versus non-NPSLE	13	1,110	0.29 (0.15–0.48)	0.80 (0.74–0.85)
All diffuse neuropsychiatric manifestations versus focal neurologic events	12	406	0.26 (0.14–0.43)	0.70 (0.50–0.84)
Psychosis and/or mood disorder versus other diffuse neuropsychiatric manifestations	12	228	0.28 (0.15–0.46)	0.75 (0.57–0.88)
Patients with psychosis and/or mood disorder versus all other lupus patients	12	1,322	0.27 (0.14–0.47)	0.80 (0.72–0.86)

* Weighted sensitivity and specificity were determined according to the random-effects model. Between-study heterogeneity was statistically significant for all comparisons ($P < 0.01$). 95% CI = 95% confidence interval; NPSLE = neuropsychiatric systemic lupus erythematosus.

using ELISA (Table 2). In the random-effects model, the overall weighted sensitivity and specificity estimates for the diagnosis of NPSLE were 26% (95% CI 15–42%) and 80% (95% CI 74–85%), respectively (Table 2).

Diagnostic performance for neuropsychiatric disease appeared to be somewhat better in studies that used Western blotting to detect anti-P antibodies (summary sensitivity 36% [95% CI 16–63%]; summary specificity 84% [95% CI 70–92%]), but significant between-study heterogeneity was still present ($P = 0.0001$ for heterogeneity in sensitivity estimates and $P = 0.0007$ for heterogeneity in specificity estimates), and data were too limited to be conclusive (4 studies; 424 patients). Test performance was poor for NPSLE in Asian patients (4 studies; 317 patients, yielding a summary sensitivity of 55% [95% CI 45–65%] and a summary specificity of 68% [95% CI 59–76%]). The weighted specificity tended to be higher in all other lupus patients, which were mostly of European descent, but there was low sensitivity (9 studies; 1,023 patients, yielding a summary sensitivity of 17% [95% CI 9–32%] and a summary specificity of 85% [95% CI 81–88%]).

SROC analyses suggested similar performance for identifying SLE-induced neuropsychiatric disease. Weighted and nonweighted curves were practically coincident (Figure 1A). Anti-P antibodies had an almost equally meager discriminating ability for the diagnosis of either psychiatric syndromes or other forms of neuropsychiatric involvement in SLE (Table 2). Weighted random-effects independent estimates stand very close to the weighted SROC curves for these comparisons (Figures 1B–D), suggesting that they are appropriate approximations of the overall diagnostic performance. Statistically significant asymmetry was found in all these curves (Figure 1), indicating that an improvement in specificity was accompanied by a disproportionately large decrease in sensitivity.

Within the group with NPSLE (Table 2), anti-P antibody testing could not accurately discriminate patients presenting with diffuse manifestations from those presenting with focal events (summary sensitivity 26%; summary specificity 70%) (Figure 2A) or patients presenting with psychiatric disorders from those presenting with any other diffuse symptom (summary sensitivity 28%; summary specificity 75%) (Figure 2B). Test characteristics remained unchanged for the identification of patients with psychiatric disorders compared with all other lupus patients (with or without neuropsychiatric dysfunction) (Table 2). Significant asymmetry was found in the corresponding SROC curve (Figure 2C), implying that an improvement in specificity was accompanied by an uneven, large decrease in sensitivity.

Findings of additional analyses. Our search of the 3 databases identified a total of 306 potentially relevant articles, of which 243 studies were excluded upon reading the titles and abstracts. Another 39 studies were excluded after reviewing the complete reports: 8 were editorials, comments without original data, or review articles, 11 were case reports, 7 studies presented duplicate or overlapping data, 8 evaluated anti-P antibody testing for other SLE manifestations or other autoimmune diseases, 3 focused on isolated neuropsy-

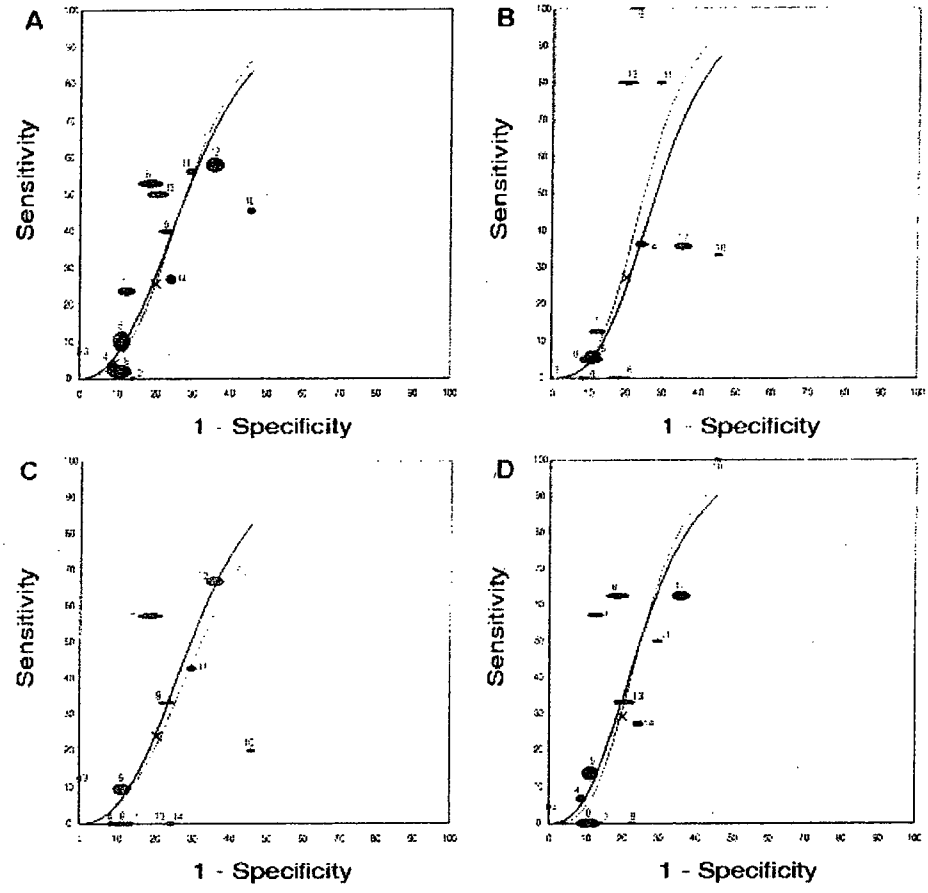

Figure 1. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus (NPSLE). Results are from the main analysis. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Numbers beside the ellipses are study identification numbers and correspond to those shown in Table 1. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A,** NPSLE overall versus non-NPSLE. **B,** Psychosis and/or mood disorder versus non-NPSLE. **C,** Other diffuse neuropsychiatric manifestations versus non-NPSLE. **D,** Focal neurologic events versus non-NPSLE.

chiatric syndromes, and 2 provided insufficient data for calculating the sensitivity and specificity in any comparison considered.

Twenty-four additional publications (6,8–13,15–20,22,23,25–29,31–34) were retrieved from the database search, representing a total of 38 studies involving 3,713 lupus patients. Nevertheless, data for the comparison of NPSLE versus non-NPSLE groups were available in only 18 of the 24 additional studies; data for other comparisons were available in even fewer reports (Table 3). The results were consistent with those derived from the collaborative meta-analysis (Table 3 and Figure 3), but between-study heterogeneity was always considerable (Table 3). The overall weighted sensitivity and specificity estimates for identifying patients with NPSLE were 28% (95% CI 22–35%) and 80% (95% CI 75–85%), respectively. The SROC curve for this comparison was located very close to the diagonal, indicating poor diagnostic performance (Figure 3A). The overall sensitivity for psychosis, mood disorder, or both was slightly

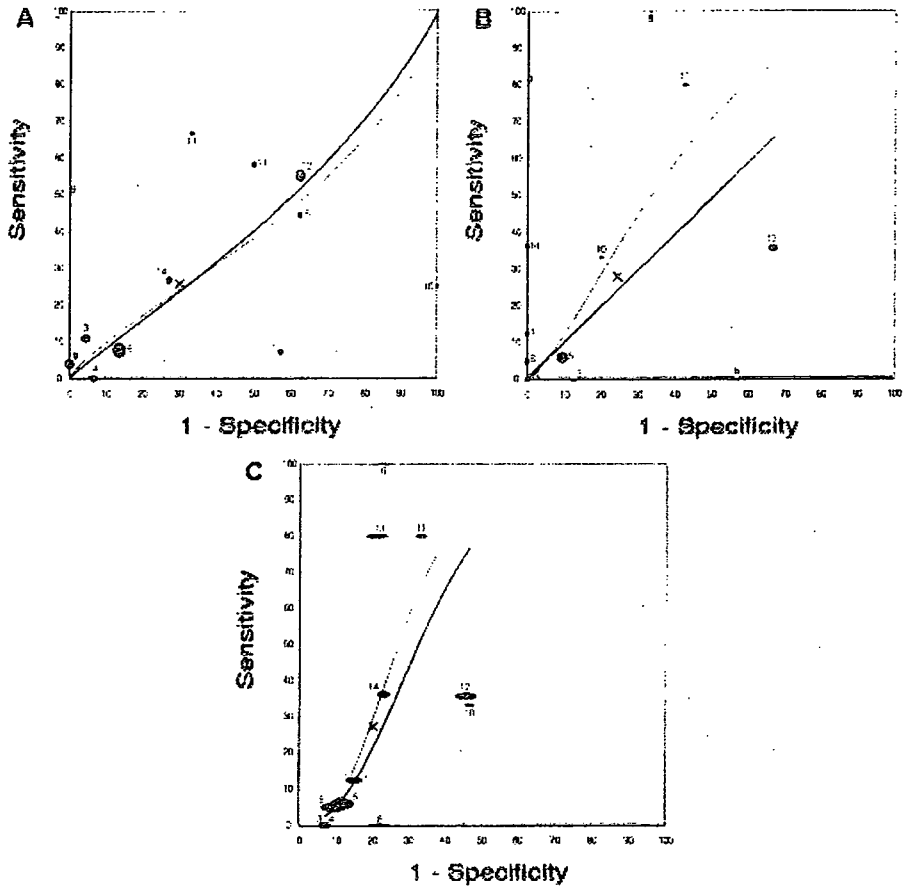

Figure 2. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Numbers beside the ellipses are study identification numbers and correspond to those shown in Table 1. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. A, All diffuse neuropsychiatric manifestations versus focal neurologic events. B, Psychosis and/or mood disorder versus other diffuse neuropsychiatric manifestations. C, Patients with psychosis and/or mood disorder versus all other lupus patients.

improved, but it was still suboptimal (42%), and the specificity remained essentially the same (81%). There was still significant asymmetry in the SROC curves for the diagnosis of psychiatric disorders (Figures 3B and C). Anti-P antibody testing was not more accurate when used to discriminate active NPSLE from non-NPSLE (Table 3 and Figure 3D). Weighted and nonweighted SROC curves were almost coincident in all these contrasts (Figure 3).

Findings of other sensitivity analyses. Analyses limited to studies that used the ACR criteria for NPSLE yielded similar results. The weighted sensitivity for NPSLE overall was 29% (95% CI 17–45%) and the weighted specificity was 79% (95% CI 73–84%). Analyses excluding studies that did not specify blinding yielded a sensitivity of 25% (95% CI 13–43%) for the diagnosis of NPSLE and a specificity of 79% (95% CI 70–86%). Likewise, the diagnostic performance of anti-

Table 3. Summary results of additional analyses that included published studies from database searches*

Comparison	No. of studies	No. of subjects	Weighted sensitivity (95% CI)	Weighted specificity (95% CI)
NPSLE versus non-NPSLE	32	2,861	0.28 (0.22–0.35)	0.80 (0.75–0.85)
Psychosis and/or mood disorder versus non-NPSLE	25	1,909	0.42 (0.30–0.53)	0.81 (0.76–0.85)
Patients with psychosis and/or mood disorder versus all other lupus patients	31	3,309	0.41 (0.31–0.52)	0.81 (0.77–0.85)
Active NPSLE versus non-NPSLE	10	1,025	0.34 (0.27–0.43)	0.82 (0.74–0.87)

* Data from the studies shown in Table 1 as well as from additional studies retrieved from a search of the Medline, EMBase, and Cochrane databases are included. Weighted sensitivity and specificity were determined according to the random-effects model. Between-study heterogeneity was statistically significant for all comparisons ($P < 0.01$). 95% CI = 95% confidence interval; NPSLE = neuropsychiatric systemic lupus erythematosus.

P antibodies was largely unaffected in all other comparisons (data not shown).

DISCUSSION

This meta-analysis demonstrated with large-scale evidence that the value of anti-P antibody testing for the diagnosis of NPSLE overall or for particular disease phenotypes is negligible. No large differences in diagnostic performance with ELISA measurements or with Western blotting were discerned. Serum anti-P antibodies are detected by ELISA in less than one-third of patients with NPSLE, while 15–25% of lupus patients without neuropsychiatric involvement have this autoantibody specificity. Testing for anti-P antibody is not useful in excluding disease-mediated psychosis or mood disorder with enough certainty, since more than 60% of cases are false negative. Also, a false-positive rate of ~20% militates against the dependence on this laboratory test for diagnosing psychiatric disorders in lupus patients.

Whereas nearly all studies suggested poor diagnostic performance, the exact test performance varied substantially. Variability beyond chance could be attributed to ethnic differences in the study patients, the clinical setting, the type of assay used, differences in test thresholds, and differences in therapy at the time of testing. Anti-P antibodies were more prevalent in Asian patients with lupus than among those of other racial ancestries. This finding is consistent with the observation that their production is influenced by certain class II major histocompatibility complex alleles (8). Despite the use of uniform criteria for defining neuropsychiatric disease, the prevalence of NPSLE differed across centers. This difference probably reflects varying referral patterns at the research sites, as well as varying practice patterns for performing anti-P antibody testing in lupus patients with possible NPSLE syndromes.

The immunoassays used for anti-P antibody determination often differed in terms of the antigenic source, the conditions of protein extraction and denaturation, the nature of the coating antigen, and the carrier proteins and coupling agents used for binding antigen to the plate. The selected cutoff value designating a positive result in enzyme immunoassays could also affect the sensitivity and specificity. Nevertheless, a standardization of anti-P antibody testing is essential to avoiding technical or analytical differences among centers. Treatment with immunosuppressive drugs at the time of testing might influence the antibody response and, therefore, could also account for the discrepancies in test performance. Heterogeneity stemming from all these sources is probably unavoidable, and it reflects actual clinical practice.

Our analysis addressed heterogeneity by using a random-effects model that incorporated the uncertainty arising from between-study differences. SROC curves, which correct for variation due to differences in test thresholds across studies, were also consistent with the independently weighted estimates, and accordingly, the results of the meta-analysis should be generalizable to diverse settings.

Specific design flaws of primary studies of diagnostic tests including lack of blinding, use of different reference tests according to the results of the experimental test, and insufficient description of the population under study can lead to biased, usually optimistic estimates of diagnostic accuracy (48). Our study had the methodologic advantage of using data from adequately described lupus cohorts in which a consistent application of standardized definitions of NPSLE syndromes, and

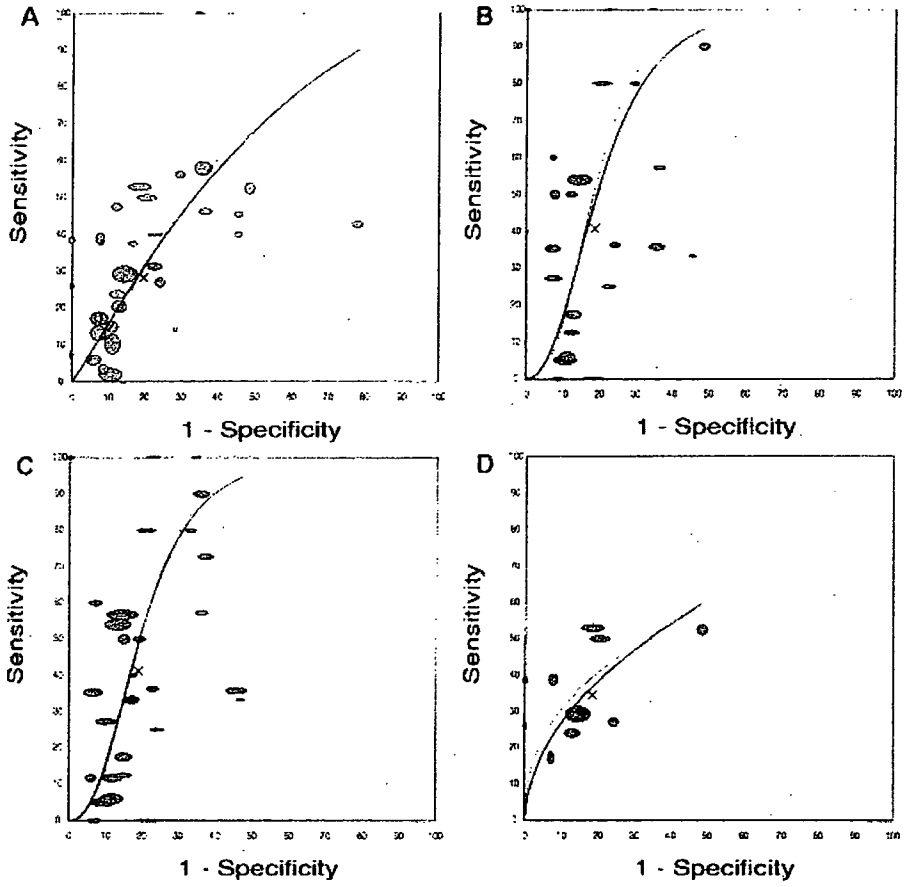

Figure 3. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus (NPSLE). Results are from sensitivity analyses that included additional published data. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A,** NPSLE overall versus non-NPSLE. **B,** Psychosis and/or mood disorder versus non-NPSLE. **C,** Patients with psychosis and/or mood disorder versus all other lupus patients. **D,** Active NPSLE versus non-NPSLE.

blinded interpretation of both the test results and the reference standard was ensured in most cases. In addition, the overall estimates did not materially change after we excluded the few studies that did not specify blinding or did not use the ACR case definitions for NPSLE.

We should acknowledge that the ACR criteria may not be a perfect reference standard for assessing the presence or absence of NPSLE syndromes in lupus patients. In fact, this classification system has been criticized for some lack of specificity; disorders such as headache, anxiety, mild cognitive dysfunction, mild depression, and polyneuropathy without electrophysiologic confirmation may not truly be NPSLE syndromes (1,49). Nevertheless, until revised criteria (49,50) are accepted and validated, the ACR case definitions constitute the best available tool with which to categorize neuropsychiatric events in SLE (4,51).

Another limitation of the study is that patients having both diffuse and focal NPSLE events were clas-

sified according to the predominant disorder. Such complex presentations might reflect a multifactorial pathogenic etiology with overlapping mechanisms (2,3,6), and therefore, we cannot completely exclude the possibility that some of these patients may have been misclassified. Nevertheless, this limitation is unlikely to have significantly affected the estimated performance, since anti-P antibodies had poor discriminating ability for all disease subtypes. Another possibility is that some patients who tested positive for anti-P antibodies could have been misclassified as non-NPSLE patients, because the disease phenotype may not have had adequate time to express itself. This seems implausible, since nervous system involvement occurs within the first 2 years of disease onset in most patients and rarely presents late (52). The median disease duration in the study population was 7.3 years. A further explanation for anti-P positivity in patients without neuropsychiatric involvement could be the presence of other manifestations that have been linked with these antibodies, such as liver or renal disease, but here, the evidence is far sparser than for NPSLE (53–56). Titers may also fluctuate with the course of the disease (53,55), making the appraisal of a positive or negative result even more difficult. Finally, the diagnostic ability of anti-P antibody in the cerebrospinal fluid needs further study, although it seems to be even more limited than the ability of serum autoantibodies to detect NPSLE (6,16,26,27).

The overall sensitivity of anti-P antibodies for identifying lupus patients with disease-associated psychosis, mood disorder, or both was slightly improved when further published studies were included in the analyses. However, these estimates have widely overlapping confidence intervals with those obtained from the collaborative meta-analysis. Yet, methodologic weaknesses frequently encountered in the relevant reports, such as the use of less strict definitions of psychiatric disorders and the lack of blinding during test or reference standard interpretation, might well have led to inflated sensitivity estimates.

Although the extent of publication bias in diagnostic studies is unknown, we should be aware that studies that failed to show a diagnostic value for anti-P antibodies may have remained unpublished. If this is so, the true diagnostic performance of anti-P antibodies may be even worse than what was demonstrated in this analysis.

There is increasing interest in synthesizing diagnostic information on tests used in autoimmune diseases (57–59). Based on the categorization standards adopted in meta-analyses conducted by the ACR Ad Hoc Committee on Immunologic Testing, the diagnostic performance of anti-P antibodies would be rated as "not useful" for most of the comparisons that we examined, since the observed sensitivity and specificity estimates would correspond to a positive likelihood of ratio <2 and a negative likelihood ratio of >0.5. Previous meta-analyses (57–59) have been based on published data, whereas in our meta-analysis, we made an effort to include the primary investigators and to obtain additional unpublished and prospectively accrued data. It is important to encourage such collaborations in an attempt to obtain large-scale unbiased evidence in the field.

In conclusion, anti-P antibody testing has negligible diagnostic utility for NPSLE overall or for particular neuropsychiatric presentations of SLE. A consortium approach with synthesis of standardized data through a comprehensive meta-analysis may offer a powerful method by which to rigorously evaluate diagnostic tests in SLE. Such an approach could limit health care costs by preventing unnecessary testing.

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