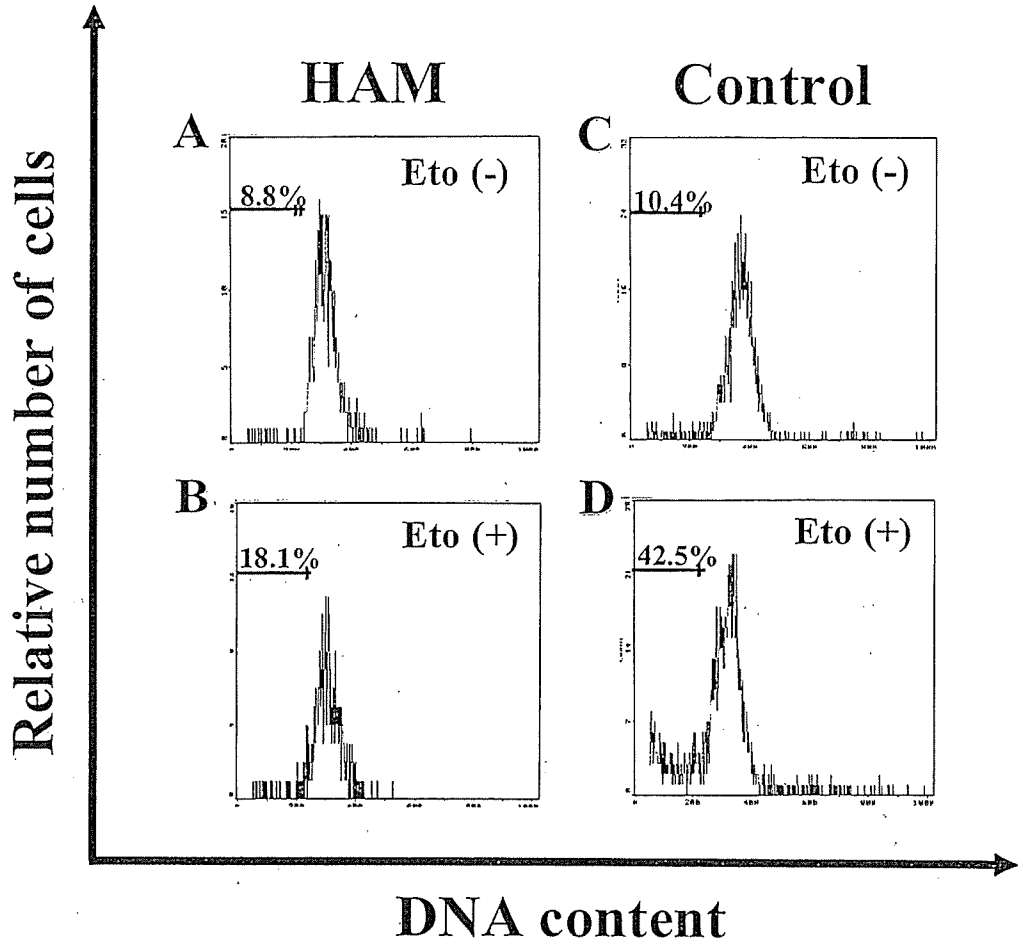
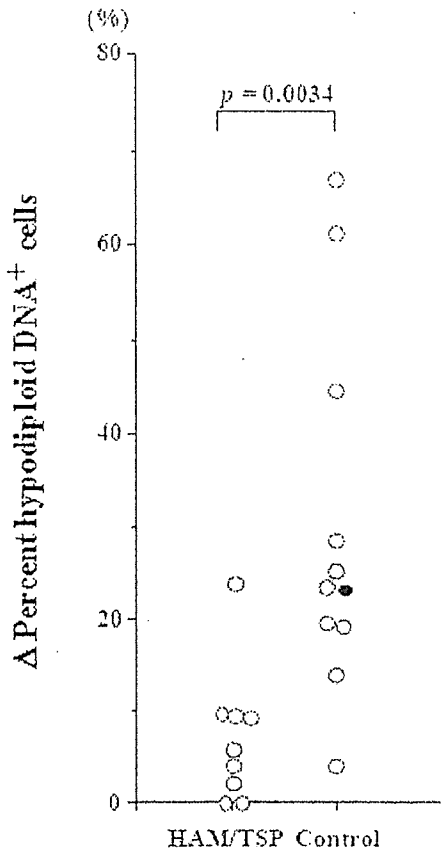
A balance between apoptotic and anti-apoptotic signals determine survival and death of lymphocytes . Two independent pathways operate in the process of apoptosis [99, 100]. The first is the death receptor-induced apoptotic death pathway including Fas, while the second is the mitochondrial death pathway. The latter is mediated by the release of cytochrome c from the mitochondria following cellular stress, such as anti-cancer drugs and UV irradiation. The Bcl-2 family is composed of three subfamilies, such as Bcl-2, Bax and BH3 [101, 102]. Among these, the Bcl-2 subfamily includes Bcl-2, Bcl-xL and Bcl-w, which have anti-apoptotic activity, enhance the survival of lymphocytes by inhibition of cytochrome *c* release from the mitochondria [103].

In order to clarify the mechanisms of the long-standing perpetuation of a chronic inflammatory state in the spinal cords of patients with HAM/TSP, we examined the resistance to apoptosis of the peripheral blood $CD4^+$ T cells induced by the anti-cancer drug, etoposide. This compound is known to induce mitochondria-dependent apoptosis through the release of cytochrome *c* [104]. In addition, we analyzed the expression of anti-apoptotic proteins, Bcl-xL proteins, on the peripheral blood $CD4^+$ cells of HAM/TSP patients, by using Western blot [105].

In a representative case (figure 21a), the percentage of hypodiploid DNA^+ cells in the peripheral blood $CD4^+$ cells cultured with etoposide was lower in the HAM/TSP patient than the control patient. We determined the percentage of hypodiploid DNA^+ cells in each culture with or without etoposide. Δ% hypodiploid DNA^+ cells, representing the effect of etoposide, was determined as follows: Δ% hypodiploid DNA^+ cells = the percentage of hypodiploid DNA^+ cells in each culture with etoposide - the percentage of hypodiploid DNA^+ cells in each culture without etoposide. As shown in figure 21b, comparison of the susceptibility to apoptosis induced by etoposide between HAM/TSP and control patients showed that Δ% hypodiploid DNA^+ cells in the peripheral blood $CD4^+$ T cells was significantly smaller in patients with HAM/TSP (7.2 $\pm$ 2.5%) than in control patients including one anti-HTLV-I-seropositive carrier (29.9 $\pm$ 5.9%), indicating that the peripheral blood $CD4^+$ T cells of HAM/TSP patients are resistant to etoposide-induced apoptosis.


HAM
Control
A
Eto (-)
8.8%
C
Eto (-)
10.4%
B
Eto (+)
18.1%
D
Eto (+)
42.5%
Relative number of cells
DNA content

a)



b)

Figure 21. Apoptosis of peripheral blood CD4$^+$ T cells induced by etoposide. a) A representative flow cytometry analysis of hypodiploid DNA$^+$ cells in peripheral blood CD4$^+$ T cells, treated with 10 μM of etoposide [Eto (+)] or without etoposide [Eto (-)], of a representative HAM/TSP patient and control. A: Eto (-) in HAM/TSP patient; B: Eto (+) in HAM/TSP patient; C: Eto (-) in control; D: Eto (+) in control. Percentage numbers indicate the percentage of hypodiploid DNA$^+$ cells. b) Comparison of Δ% hypodiploid DNA$^+$ cells in peripheral blood CD4$^+$ T cells treated with 10 μM/mL of etoposide between 9 HAM/TSP patients and 11 controls. Δ% hypodiploid DNA$^+$ cells is significantly lower in HAM/TSP patients than in the controls, indicating that peripheral blood CD4$^+$ T cells of HAM/TSP patients are resistant to etoposide-induced apoptosis. Δ% hypodiploid DNA$^+$ cells = the percentage of hypodiploid DNA$^+$ cells in each culture with etoposide - the percentage of hypodiploid DNA$^+$ cells in each culture without etoposide. Closed circle: an anti-HTLV-I-seropositive carrier. Mann-Whitney's U-test was used for statistical analysis. Quotation from Ref. 105.

As shown in Western blot analysis (figure 22a), expression of Bcl-xL protein in the peripheral blood CD4$^+$ T cells was higher in HAM/TSP patients than in the controls. Furthermore, the ratio of Bcl-xL protein to β actin (ER) in HAM/TSP patients was significantly higher than in the controls (figure 22b). These results imply that the expression of Bcl-xL protein, which is an anti-apoptotic protein, is up-regulated in the peripheral blood CD4$^+$ T cells of HAM/TSP patients. Using Western blot analysis, we also examined the expression of

Bcl-2 protein and X chromosome-linked inhibitor of apoptosis protein (XIAP), which are other anti-apoptotic Bcl-2-related proteins, and an inhibitor of caspases (caspase-3, -7, and -9) [106], respectively. There were no significant differences in the expression of both anti-apoptotic proteins in the peripheral blood $CD4^+$ T cells between HAM/TSP patients and controls (data not shown).

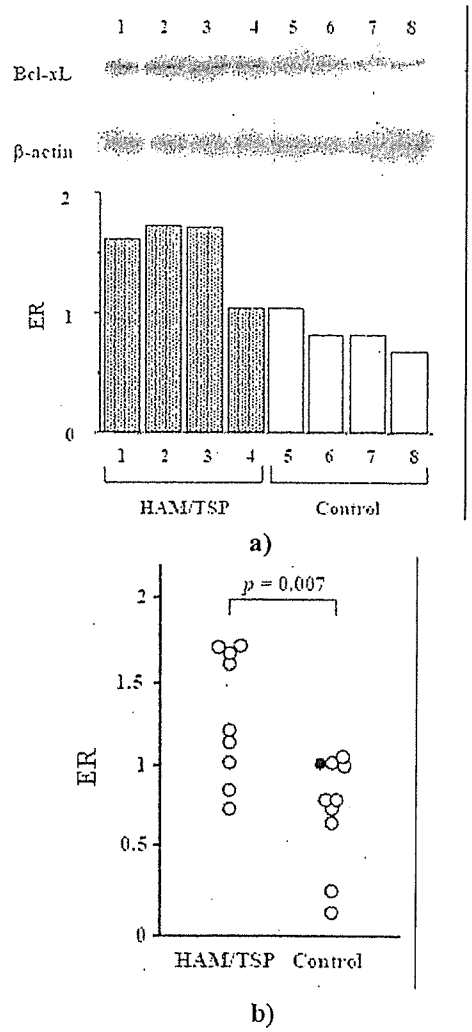


Figure 22. Western blot analysis of Bcl-xL protein expression on peripheral blood $CD4^+$ T cells. a) A representative Western blot analysis of Bcl-xL protein expression in peripheral blood $CD4^+$ T cells in 4 HAM/TSP and 4 control patients. Expression level of Bcl-xL protein in peripheral blood $CD4^+$ T cells, indicated as ER, was higher in HAM/TSP patients than in the controls. b) Comparison of ER of Bcl-xL protein expression on peripheral blood $CD4^+$ T cells between 9 HAM/TSP patients and 10 controls. The expression ratio (ER) in HAM/TSP patients was significantly higher than that in the controls. ER was determined as follows: ER = densitometric counts in each Bcl-xL protein / densitometric counts in each β-actin. Closed circle: an anti-HTLV-I-seropositive carrier. Mann-Whitney's U-test was used for statistical analysis. Quotation from Ref. 105.

In this study, we demonstrated that the peripheral blood CD4$^+$ T cells of HAM/TSP patients are resistant to apoptosis induced by etoposide, which induces mitochondria-dependent apoptosis [104], mediated by up-regulation of Bcl-xL expression. These findings strongly suggest that the peripheral blood CD4$^+$ T cells of HAM/TSP patients can evade local apoptotic machinery in the spinal cords to induce long-standing perpetuation of a chronic inflammatory state. Although we showed that there were no significant differences in the expression of both Bcl-2 and XIAP in the peripheral blood CD4$^+$ T cells between HAM/TSP patients and controls, it was reported that constitutive expression of Bcl-xL, but not Bcl-2, through NF-κB was associated with resistance to apoptosis after deprivation of IL-2 in IL-2-dependent T-cell line transfected with HTLV-I tax [107]. Although HTLV-I tax is a powerful activator of NF-κB [108], activation of NF-κB by tax protein in HTLV-I-infected cells can render the cells resistant to apoptosis by inhibiting the caspase cascade [109]. Therefore, the resistance to apoptosis induced by etoposide concomitant with up-regulation of Bcl-xL expression in the peripheral blood CD4$^+$ T lymphocytes of HAM/TSP patients might be related to NF-κB activation based on high HTLV-I proviral load in patients with HAM/TSP, although we did not actually analyze the degree of NF-κB activation in the peripheral blood CD4$^+$ T cells in this study. In addition, it is unclear whether the resistance to apoptosis induced by etoposide mediated by the up-regulated expression of Bcl-xL in the peripheral blood CD4$^+$ T cells of HAM/TSP patients are based on only HTLV-I-infected cells or not. Indeed, NF-κB could also be activated by inflammatory cytokines, such as TNF-α and lymphotoxin [110], the expressions of which are up-regulated in the peripheral blood T cells of HAM/TSP patients. Therefore, the up-regulated state of the expression of these inflammatory cytokines might induce NF-κB activation even in non-HTLV-I-infected T cells of HAM/TSP patients. Thus, in the peripheral blood CD4$^+$ T lymphocytes of HAM/TSP patients, activation of NF-κB might be amplified reciprocally in HTLV-I-infected and non-HTLV-I-infected cells. Although the Fas-mediated pathway is another apoptotic death pathway [99], there are several reports that HTLV-I-infected T cells are also resistant to Fas-mediated apoptosis [111, 112]. Considered together with the results of the present study, it is reasonable to suggest that HTLV-I-infected cells in the peripheral blood CD4$^+$ T cells of HAM/TSP patients are strongly resistant to both Fas and stress-induced pathways of apoptotic cell death. Therefore, the resistance to apoptosis of HTLV-I-infected cells seems to strongly contribute to the long-standing perpetuation of a chronic inflammatory state induced by bystander mechanisms of the interactions between HTLV-I-infected CD4$^+$ T cells and HTLV-I specific CD8$^+$ cytotoxic T cells in the spinal cord lesions of HAM/TSP patients.

Conclusion

In this review article, we demonstrated that HTLV-I-infected CD4$^+$ T cells of the peripheral blood of HAM/TSP patients have the potential to trigger the pathological process in the spinal cords based on the increased transmigrating activity to the tissues which possess the characteristics of activated Th1 on the background of systemic Th1 activation. Therefore, it is conceivable that the increase of HTLV-I-infected Th1 cells in the peripheral blood is strongly

involved in the first step of the immunopathogenesis of HAM/TSP. In addition, our data strongly suggest that the resistance to apoptotic signals of the peripheral blood $CD4^+$ T cells, including HTLV-I-infected cells of HAM/TSP patients, contributes to the maintenance of long-standing chronic inflammation in the spinal cords of HAM/TSP patients.

However, how activation of Th1 is induced in the peripheral blood HTLV-I-infected cells of HAM/TSP patients? How high HTLV-I proviral load is induced in the peripheral blood of HAM/TSP patients? Although we proposed that activation of the p38 MAPK signaling pathway functions as one of the mechanisms to induce both abnormalities in HAM/TSP patients, the exact mechanisms of how these abnormalities are induced in the peripheral blood of HAM/TSP patients remain unresolved. Since the discovery of HAM/TSP, over 20 years have passed. During that period, numerous findings have been reported in the research field of HAM/TSP [4, 113, 114]. Unfortunately, these findings have not translated into an optimal therapeutic strategy against HAM/TSP. A therapeutic strategy that manages to decrease or delete HTLV-I-infected cells seems to be critical. Therefore, further investigations are needed to clarify the exact mechanisms by which HTLV-I-infected Th1 cells are increased in the peripheral blood of HAM/TSP patients.

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神経系感染症が疑われたとき

ポイント

- 発熱を伴った頭蓋内圧亢進症状，脳実質障害があれば，髄膜炎，脳炎を積極的に疑うべきである．
- 食欲不振，倦怠感といった不定愁訴（結核性髄膜炎など）や精神症状（単純ヘルペス脳炎など）が発熱に先行する場合があり注意を要する．
- ときに，発熱が前景に立たないで性格変化や痴呆症状が中核をなす一群の神経感染症がある（スローウイルス感染症やプリオン病など）．
- 神経系感染症を疑う場合，髄液検査は病原診断へと導く第一歩である．ルーチンの検査でも病原体の種類を推察するにあたってある程度のところまで絞り込める．
- 一般的に画像検査（頭部 CT および MRI）や脳波検査では特異的な異常はないことが多いが，単純ヘルペス脳炎やプリオン病などではこれらの検査で特徴的な所見がみられることがある．

Ⅰ どういう症状が出たら神経系感染症を疑うか？

神経系感染症は中枢神経系および末梢神経系感染症があり，症状はその障害部位に応じて多種多彩であるが，多くの場合発熱という炎症所見を伴った神経症状をみたら感染症を疑うべきである．

神経系感染症のうち，各種髄膜炎・脳炎が日常臨床で遭遇する最も頻度の高い疾患であるが頭痛，悪心，嘔吐といった頭蓋内圧亢進症状があれば髄膜炎を，加えて意識障害，失見当識・異常行動といった精神症状，

痙攣などの脳実質障害があれば，脳炎を積極的に疑うべきである．

◉食欲不振，倦怠感といった不定愁訴（結核性髄膜炎など）や精神症状（単純ヘルペス脳炎など）が発熱に先行する場合があり注意を要する．

◉例外的には，発熱が症状の前景に立たないで，原因の同定できない性格変化，認知障害，痴呆症状などが中核症状であれば，スローウイルス感染症，HIV 脳症，プリオン病などを考える必要がある．

参考 本邦における神経系感染症関係のデータベース

神経系感染症関係の発症動向の週報や過去の統計などが国立感染症研究所・感染症情報センター http://idsc.nih.go.jp/index-j.html のデータベースより入手可能である．また，昨今は交通手段のめざましい発達により神経系感染症の領域でも新興感染症に注意を払うべき時代になっている．ぜひこのデータベースを活用されたい．

Ⅲ どのように診断を進めていくか？

◉図 1－6－1 に神経系感染症の病原診断のためのフローチャートを示す．全身性疾患の把握と免疫不全状態やワクチン接種の有無などを含めた正確な病歴聴取と局在診断のために正しく神経学的所見をとることが肝要である．

◉同時に皮疹，水疱などの皮膚症状，耳鼻咽喉科的な異常の有無，上気道炎様症状，呼吸器症状，消化器症状などの全身状態の把握も病原診断のための一助になる．

◉季節も重要である．一般的にウイルス性髄膜炎の中で最も頻度が高いエンテロウイルスによる髄膜炎の流行季節は初夏から初秋にかけてであり，日本脳炎は夏から初秋にかけてである．

◉髄膜炎や脳炎の場合，必ずしも髄膜刺激症状（項部硬直，ケルニッヒ徴候など）が目立たない場合もある．例えば，結核性髄膜炎や真菌性髄膜炎は脳底部髄膜炎の形をとるので，しばしば髄膜刺激症状がはっきりしない場合があるので注意を要する．

◉一般的に，髄膜炎では髄膜刺激症状のみで脳の局所徴候は伴わないこと

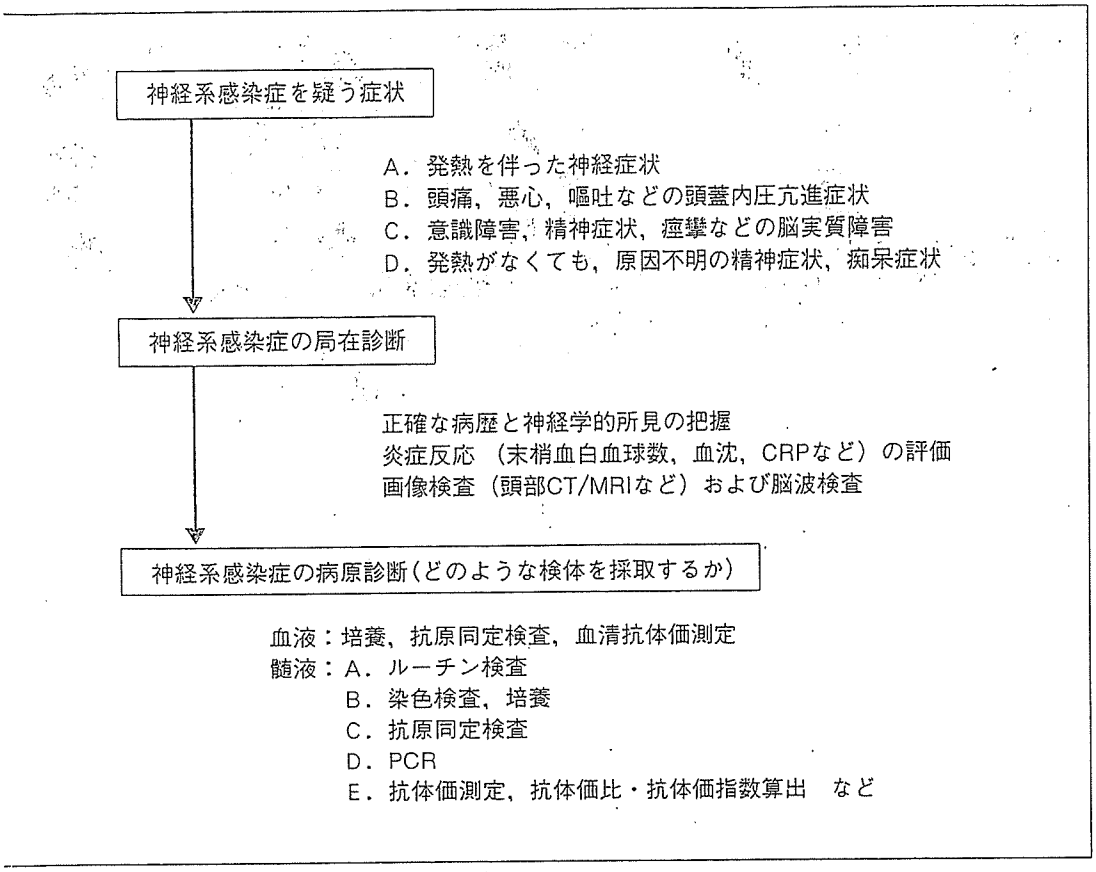

図1－6－1　神経系感染症の診断から病原体検索までのフローチャート

が多いが，動眼神経麻痺などの脳神経麻痺や片麻痺などの局所徴候が認められる場合には，結核性髄膜炎，真菌性髄膜炎，あるいは脳膿瘍などの存在を考える必要がある．

中枢神経系感染症では特異的な病型として，亜急性硬化性全脳炎（SSPE）や進行性多巣性白質脳症（PML）などのスローウイルス感染症の一群，HIV 脳症，プリオン病があり，原因がよくわからない精神症状，知能低下，認知機能の低下などがある場合は，これらの疾患も考える必要がある．

プリオン病や SSPE では不随意運動の一つであるミオクローヌスがしばしば出現する．

感染を示唆する炎症所見（末梢血白血球数，CRP など）はウイルス性髄膜炎・脳炎では異常を示さないことが多い．

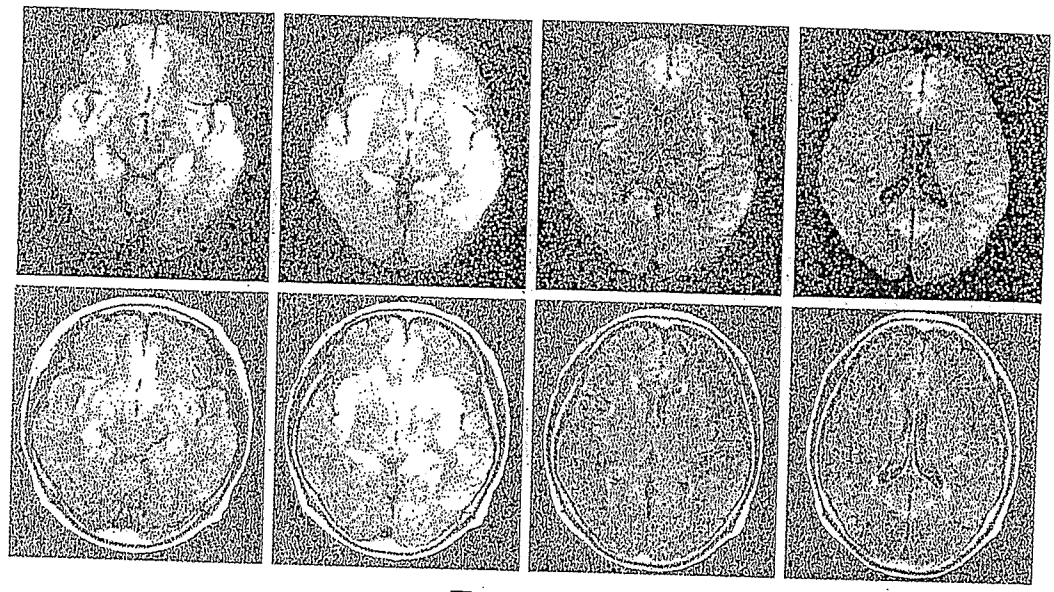

図1－6－2 a
単純ヘルペス脳炎患者（64歳，女性）の頭部MRI拡散強調画像（上段）とFLAIR画像（下段）．帯状回，島，側頭葉皮質および側頭葉内側で高信号を呈している．

- 腰椎穿刺による髄液検査は髄膜炎・脳炎の起因病原体の確定のための第一歩である．ただし，腰椎穿刺前に頭部CT検査などの画像検査を施行した方が望ましい．水頭症や脳膿瘍の合併などが疑われる場合には，腰椎穿刺は脳ヘルニアの危険性を考えて慎重であるべきである．
- 髄膜炎・脳炎の頭部CTおよびMRI検査においては必ずしも異常所見が見出されるとは限らないが，脳浮腫のための脳室の狭小化，脳溝の不鮮明化，脳槽の閉塞などがみられることがある．また，合併症として水頭症が生じれば脳室の拡大がみられたり，血管炎による脳梗塞の所見がみられることがある．
- 結核性髄膜炎の場合，脳底槽で造影剤による増強効果がみられたり，結核腫が認められることがある．
- 単純ヘルペス脳炎では前頭葉・側頭葉においてCT上低吸収域の所見やMRI上拡散強調画像，FLAIR画像，T2強調画像において異常信号域を認めることがある（図1－6－2 a）．また，日本脳炎では，大脳基底核部にMRI上T2強調画像において異常信号を認める場合がある．
- プリオン病の代表疾患である孤発性クロイツフェルト-ヤコブ病（CJD）では頭部MRI拡散強調画像において皮質病変を発病の早期に検出できることがあり早期診断に有用である（図1－6－3 a）．また，一部ではT2

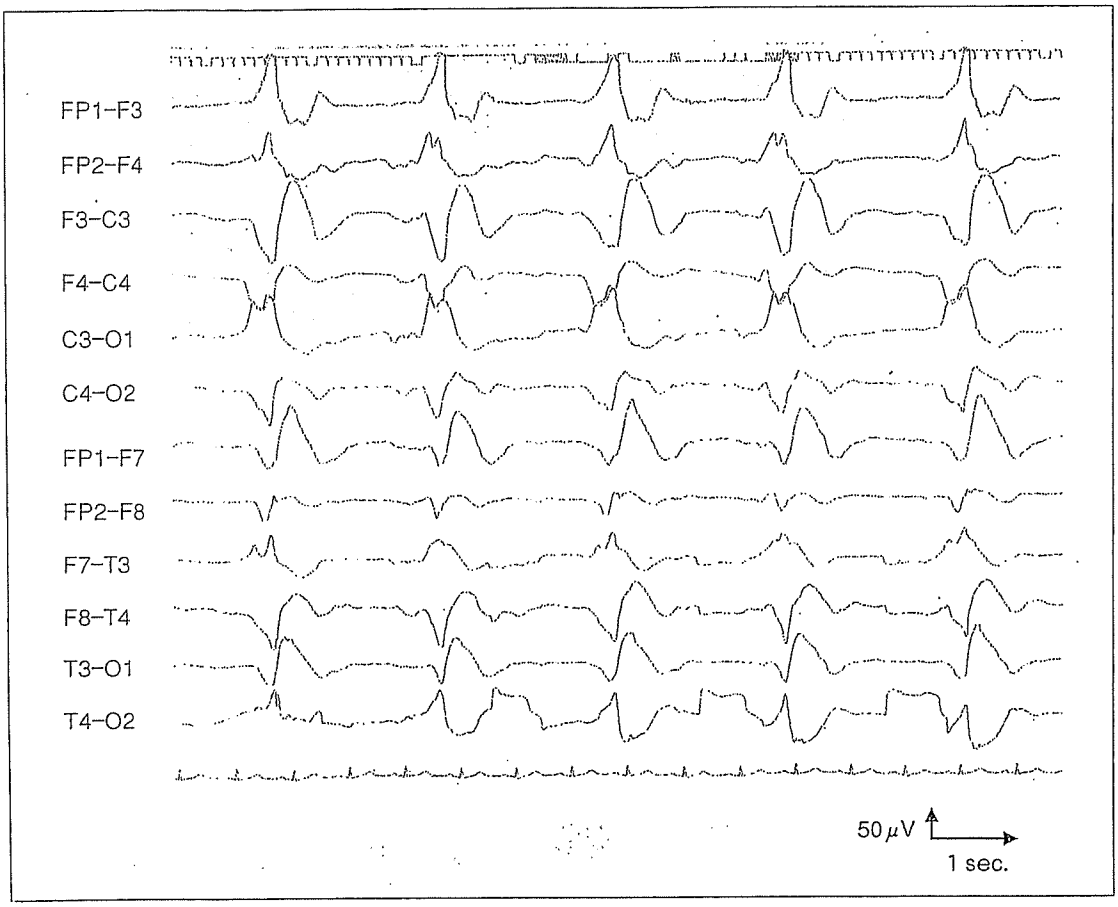

図1-6-2 b

同患者脳波検査でみられた周期性同期発射 periodic synchronous discharge (PSD). 全誘導同期性に周期的・連続性に出現している.

強調画像において発病の比較的早期より大脳基底核，視床に高信号域がみられることがある．また，SPECT で発病の早期より大脳の血流低下が検出される（図1-6-3 b）.

脳波検査は診断的特異性はあまりないが，ウイルス性脳炎の場合は汎発性徐波異常を呈することが多い.

単純ヘルペス脳炎ではほとんど全例で異常がみられ，前頭部・側頭部を中心に局所性徐波異常あるいは焦点性スパイクを呈したりする．また，周期性同期発射 periodic synchronous discharge (PSD)（図1-6-2 b）や周期性発射が一側性にみられる周期性一側てんかん形発射 periodic lateralized epileptiform discharges (PLEDs) が出現すれ、

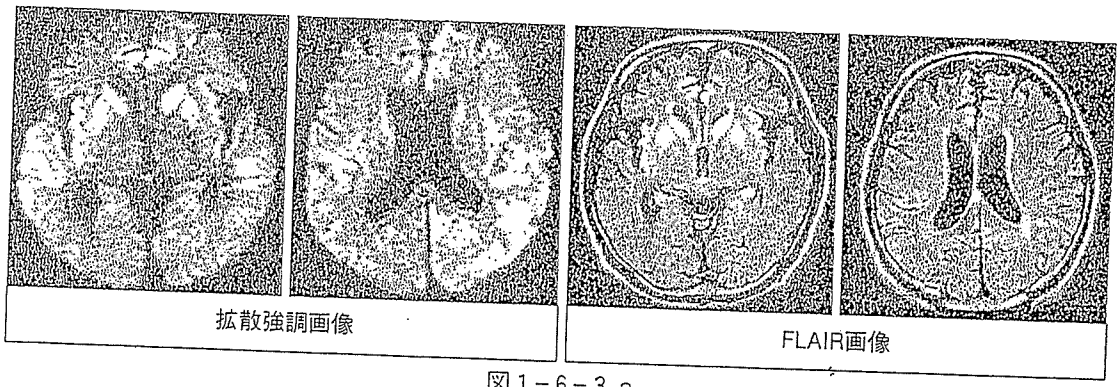

図1-6-3 a

孤発性CJD患者（67歳，男性）の発病早期の頭部MRI拡散強調画像とFLAIR画像．拡散強調画像では前頭葉，後頭葉を中心に皮質領域に高信号がみられる．また，大脳基底核領域にも高信号がみられる．

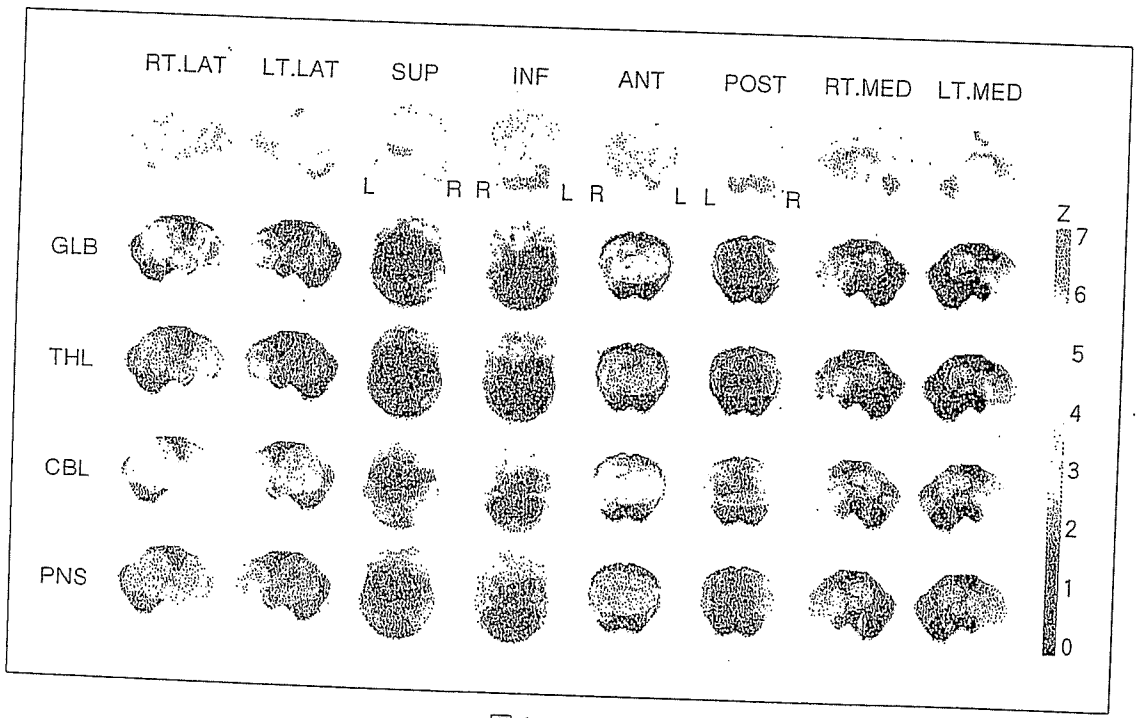

図1-6-3 b

同患者の ^{123}I-IMP SPECT所見．全般的な脳血流低下がみられる

ば診断するにあたっての意義は大きい．PSDの所見はCJDにおいてもミオクローヌスが出現する頃になるとみられることがある．

Ⅲ どんな検体を採取するか？

- 神経系感染症が疑われる場合には検体を採取し，病原診断を行う．
- 血液検査（血算，血沈，CRP，血液生化学検査など）と咽頭ぬぐい液・喀痰・尿・血液培養を行う．
- 各種髄膜炎・脳炎ではルーチンの髄液検査でも起因する病原体の種類を推察するにあたってある程度のところまで絞り込める．その際，大切なポイントは増加している白血球の種類（多核球か，単核球か）と糖の低下の有無である（必ず同時に血糖も測定しておくことが必要である）．ただし，すでに抗生物質などによる治療が開始されている例では典型的な所見にならないこともありうるので注意を要する．
- 採取された髄液は遠沈し，グラム染色，抗酸菌染色，墨汁染色を行うとともに，培養に提出する．すでに抗生物質が投与されている例や結核性あるいは真菌性の症例では必ずしも検出率は高くないということを認識しておくべきである．
- 細菌の菌体抗原を同定することができるキット（肺炎球菌，髄膜炎菌，インフルエンザ菌，B 群溶連菌など）やクリプトコッカスの莢膜多糖抗原を検出するキットが市販されていて，髄液にても検査可能である．
- 病原体の遺伝子を増幅して検出する感度と特異性の高い検査法として polymerase chain reaction（PCR）法がある．最近では，感度と特異性の高い nested PCR 法も開発されている．しかし，プライマーの設定，検出感度，検査時期などの問題点がある．また，false negative や false positive の結果に注意が必要である．
- PCR 法において髄液でも結核菌，クリプトコッカス，単純ヘルペスウイルス（1 型，2 型），水痘・帯状疱疹ウイルス，EB ウイルス，サトメガロウイルス，日本脳炎ウイルス，エンテロウイルスなどで検査可能である．
- 多くの subtype を有するエンテロウイルスではウイルス RNA の共通の配列の部分を増幅する RT－PCR 法によって検出することが可能になっている．
- ウイルス性髄膜炎・脳炎の場合，血清ウイルス抗体価が 2 週間間隔で 4 倍以上の上昇があれば，起因ウイルスの可能性が高い．ただし，エンテ