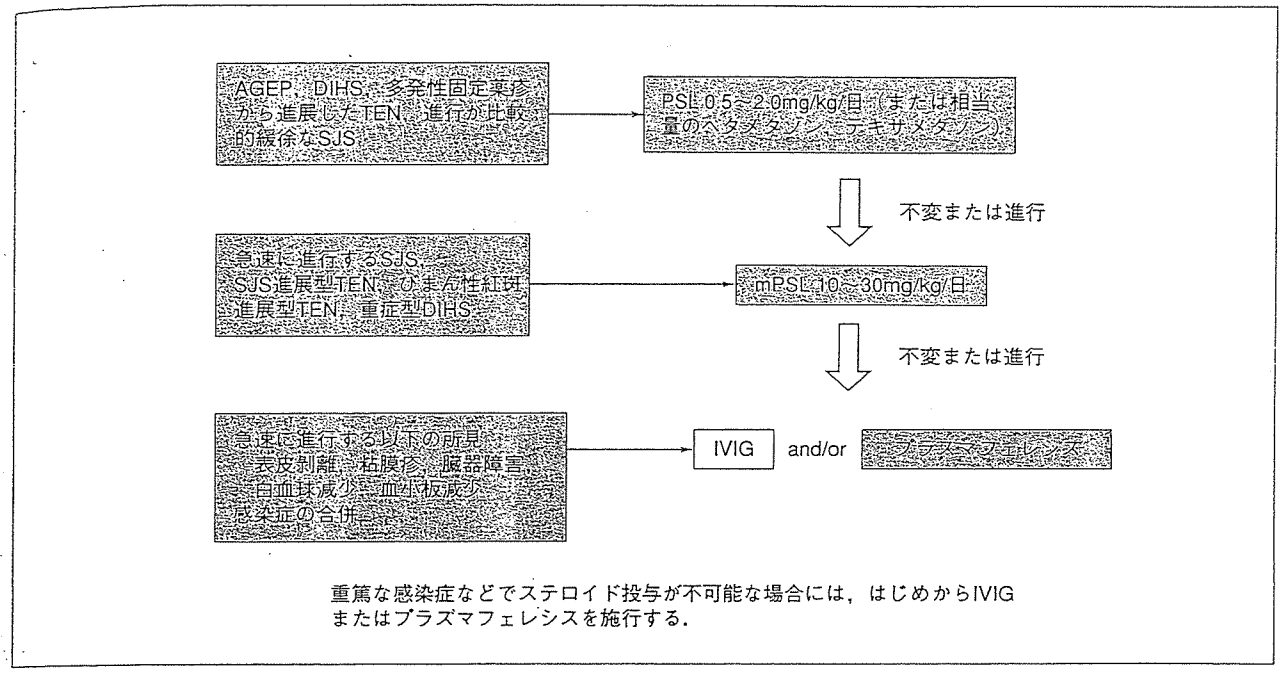

[図2] 重症薬疹の治療法の選択(試案)
AGEP：急性汎発性発疹性膿疱症，DIHS：薬剤性過敏症症候群，TEN：中毒性表皮壊死症，SJS：Stevens-Johnson 症候群，IVIG：ヒト免疫グロブリン静注療法，mPSL：メチルプレドニゾロン，PSL：プレドニゾロン

る．また，骨髄抑制により白血球減少の著しい症例では granulocyte colony-stimulating factor (G-CSF)の併用が有用である．

Ⅲ．治療法の選択とそのタイミング

治療法の選択にあたっては，糖尿病，腎機能障害などの基礎疾患や感染症の合併，年齢など多くの因子を勘案したうえ，保険適応の問題を含めた経済性も併せて検討し，選択することが求められる．図2に重症薬疹の治療法の選択についての試案を示す．

ステロイドの投与が可能な症例ではステロイド療法をまず選択する．ステロイド投与の長期化は感染症の誘発，再上皮化の遅延，消化管出血などの危険性を高めることから，進行がみられたら早期にパルス療法を行い，パルス終了後24～48時間が経過しても症状が進行する症例では効果が不十分と考え，速やかに高用量IVIGやプラズマフェレシスの併用を行う．ステロイドの投与が不可能な症例やすでに表皮剥離が広範に及んでいる症例では，はじめから高用量IVIGやプラズマフェレシスを施行する．重症化の指標としては，原因薬剤の中止後も皮疹や粘膜疹の進行が急速であること，高熱の持続，臓器障害の進行，白血球減少，感染症の併発などがあげられる．

Ⅳ．治療の実際

1. 局所療法

広範なびらん面の処置は熱傷の処置に準じて無菌操作を行う．皮膚の消毒は明らかな感染がみられる部分にとどめ微温生理食塩水などで洗浄後，アズレン含有軟膏(アズノール®)，抗生剤添加軟膏(ポリミキシンB添加アズノール軟膏®など)や，スルファジアジン銀含有剤(ゲーベンローション，ゲーベン軟膏®)などで被覆する．この際，びらん面からの薬剤の吸収を考え，腎機能障害のみられる症例ではポリミキシンB含有軟膏の大量使用は行わず，またサルファ剤による薬疹が疑われる場合にはスルファジアジン銀含有剤は使用しない．眼症状は早期には軽症であっても急速に進行がみられることがあるため，頻回に眼科医による診察を依頼する．眼結膜の治療には1日に4～6回のステロイド点眼と抗菌薬点眼(併発する

感染の予防目的)の併用，偽膜除去などが有効である．口唇，外陰部，肛囲のびらんには疼痛の抑制や癒着防止目的で軟膏剤(アズノール軟膏®など)の貼付を行う．外尿道口やその周辺に炎症がみられるときには，治癒後の瘢痕収縮を予防するため尿道カテーテルを早期より留置する．

2. ステロイド療法

TENやSJSには早期から高用量ステロイド療法(プレドニゾロン(PSL)1～2.mg/kg/日またはそれに相当する量のベタメタゾンやデキサメタゾン)の投与が進行の阻止に有用である．急速に進行する症例ではステロイドパルス療法(メチルPSL 1,000 mg/日，連日3日間)またはミニパルス療法(メチルPSL 500 mg/日，連日3日間)を行う．なお，皮疹が比較的小範囲であっても眼症状や気道症状が著しい症例においては上記の治療を施行する．多発性固定薬疹から進展したTEN，AGEP，DIHSの初期ではより少ないステロイド(PSL 0.5～1.0 mg/kg/日またはそれに相当する量のベタメタゾンやデキサメタゾン)で十分な効果がみられることが少なくなく，効果が不十分な場合に高用量のステロイドを投与する．まれではあるもののDIHSではステロイド投与はHHV-6の再活性化を促進させてウイルス性臓器障害を引き起こす危険性が否定できず，免疫抑制状態の患者では免疫グロブリンの併用などを考慮する．皮疹や粘膜疹の進行が止まったと判断されたら数日間隔で減量する．しかしながら，十分に炎症反応が治まる前に急激に減量すると皮膚粘膜症状や肝障害の再燃，白血球減少などがしばしばみられるので，慎重に減量していくことが重要である．

3. IVIG療法

Virardら[4]がTEN患者10例に発症2～5日にヒト免疫グロブリン0.2～0.75 g/kg/日を連日4日投与してその有効性を報告して以来，TENにおける高用量のIVIG療法が注目されている．その後，0.6～0.7 g/kg/日，連日4日投与とメチルPSL 1,000 mg/日，2日投与の併用や[8]，発症早期の1 g/kg/日[9]が有効であったとする報告，

[表1] 薬疹治療における高用量ヒト免疫グロブリン静注療法

施行方法
TEN，SJSに投与する場合
0.2～0.4g/kg/日，連日3～4日
症例により0.5～1.0g/kg/日，連日3日
有効例では投与開始24～48時間以内に表皮剝離の進行停止をみる
DIHSでは0.1～0.2g/kg/日，連日3日で効果をみることが多い
比較的軽症の副作用(投与開始30～60分後に出現し自然消退)
悪寒，発熱，頭痛，筋痛，顔面潮紅，血圧変動，悪心・嘔吐，頻脈，胸痛
重篤な副作用
ショック，無菌性髄膜炎，急性腎不全，血小板減少症，肺水腫

未施行例より死亡率が有意に低下したとする報告[10]，小児では0.5～1.0 g/kg/日の3日連続投与が有効であったとする報告[11]がなされたが，一方で，その有効性が認められなかったとする報告もみられる[12]．有効例の多くは投与開始24～48時間以内に明らかな症状の改善がみられたとされ，筆者らもステロイドパルス施行後も表皮剝離の拡大がみられた症例でIVIG療法(0.4 g/kg/日，連日3日)を施行し，24時間後には剝離の拡大停止とびらん面の乾燥化がみられた症例を経験している[13]．しかしながら，これらの大量投与療法は保険適応がなく，費用が高額であるため，容易に施行できないのが現状である．

DIHSでは，免疫グロブリンの低下がみられるなど免疫低下が示唆されており[5,14]，それらの患者にHHV-6に対する中和作用を主たる目的として投与される場合にはTENやSJSの治療で用いられるより少量で有効であると推察される．しかしながら使用する製品のロットにより含有される抗ウイルス抗体量が異なるため，抗HHV-6抗体が高力価のものを使用することにより，より大きな効果が期待される．表1にIVIG療法の施行方法と主な副作用を示す．

4. プラズマフェレシス

PEは遠心分離により血漿を除去し，新鮮凍結血漿(FFP)を補充する方法で，大量のFFPを必要とすることから治療コストがかかることとウイルス感染の危険性の増大が問題となる．DFPPは高分子有害物質を除去しアルブミン分画を含む自己血漿を返却する方法であり，完全な分離が困

難であることからPEに比べて除去効果が不十分であるが，FFPを使用せずアルブミン入り置換液の補充が行われることから，ウイルス感染の危険性は少ない．TENの治療法としては欧米では1980年代から，本邦では1990年代から施行され，ステロイド大量投与の無効例など重篤な症例にもその効果を発揮することが報告されている[17,18]．筆者らもこれまでステロイドパルス療法とγグロブリン投与の併用が無効であった症例に対してTENに施行し，良好な結果を得ている[19]．表2にプラズマフェレシスの施行方法と副作用を示す．

5. 合併症の対応

薬剤による肝，上下気道，消化管，腎などの臓器障害のほか，併発するDICや感染症の対応を行う．感染症は敗血症や肺炎などの細菌感染症および真菌性肺炎(アスペルギルス，カンジダ)，カリニ肺炎などを見逃さないよう注意する．DIHSでは再活性化したHHV-6の臓器への感染による腸炎，肝炎，脳脊髄炎，肺炎，膵炎などの臓器障害や，サイトメガロウイルスなど他のHHVの再活性化による臓器障害への対応も行う．

[表2] 薬疹治療におけるプラズマフェレシス

利点/欠点
PE　高い臨床効果/大量のFFPが必要，FFPによる感染症
DFPP　高分子有害物質の選択的除去/除去効果が不十分
施行回数(これまでの報告)
PE　1～6回
DFPP 連日2～4日，その後必要に応じ5～7日後に再度施行
副作用
頭痛，呼吸困難，狭心痛，血圧低下，悪心・嘔吐，蕁麻疹，発熱，ショック
DFPP　低アルブミン血症，低グロブリン血症，低カルシウム血症，高ナトリウム血症
PE　肝炎などのウイルス感染，血小板減少
死因　敗血症，DIC，消化管出血

PE：血漿交換，DFPP：二重濾過法，FFP：新鮮凍結血漿

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［ワンポイント・アドバイス］

薬疹のパッチテストでの注意点

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■パッチテスト（PT）が有用な薬疹のタイプは何かを考えよう

PTの感度は薬疹のタイプと原因薬剤によって異なる．湿疹型，固定薬疹型，紅皮症型，drug-induced hypersensitivity syndrome，toxic epidermal necrolysis型などはPTの陽性頻度が高い．

即時型反応にPTをするなどは，初歩的なミス．

■光線過敏症型薬疹では光PTが必要

光線過敏症型薬疹では光PTを行うことは基本中の基本．

■PTが陽性に出やすい薬剤と出にくい薬剤は？

PT陽性率の高い薬剤はカルバマゼピン84%，塩酸メキシレチン100%，ピロキシカム88%，アンピロキシカム68%．

PTの陽性頻度が低い薬剤はフェノバルビタール14%，アロプリノール12%，DDS 0%との報告がある（中村和子ほか：本邦薬疹患者におけるパッチテストの現況，第35回日本皮膚アレルギー学会・第30回日本接触皮膚炎学会合同学術大会）．

本来はPT陽性になりやすい皮疹型で誘発テストが陽性なのにPTが陰性の場合は，薬剤の代謝物がアレルゲンを考える．

■PTの濃度と基剤は？

PT濃度については，薬剤全体のリストはまだ作成できていない．薬剤は錠剤，細粒，注射薬など剤形の種類によって，異なる質と量の賦形剤が含まれており，どの薬品を使用してどの基剤に重量比%で希釈したかが重要である．しかし薬疹の文献にもPTの方法が詳しく記載されているものが少ない．

福田英三氏が編集された「薬疹情報」には，陽性になったPTなどの皮膚テストの惹起濃度が記載されていたが，現在の1980～2004には記載が省略されている．現実的には，この単行本などを参考に文献を集めて薬剤のPT濃度を検討して貼布する．

今後，個々の薬剤については日本皮膚アレルギー学会および日本接触皮膚炎学会で検討しリストを作成する予定である．

■スクリーニングのためのPTはどうするか？

スクリーニングテストとしては，錠剤や細粒そのものを乳鉢で細かく砕いて，基本はワセリンに練って重量比20%程度を最高濃度にして貼布する．陽性反応が刺激反応と紛らわしい場合は，濃度をさらに10%，1%，0.1%の対数希釈系列を作成して貼布する．なおルーチンとしてこの希釈系列を作成して貼布すると患者再度の通院の負担も少なく情報も多い．造影剤などの注射薬では，最高濃度として薬品そのものの濃度をPTし，溶解できる蒸留水などの溶媒に希釈するが，経皮吸収が悪いものでは，単純PTと同時にスクラッチPTを行うことで感度を上げることもできる．

■製品が陽性でも賦形剤のアレルギーを必ず念頭におく

PT陽性でも，主薬が原因であるとは断定できない．剤形の異なる同薬の含まれる薬剤をできるだけ同時にPTを行い，また，陽性となった薬剤の主薬と賦形剤を入手してさらにPTを行うこと

をすすめよう．海外では抗菌薬の一部はPT試薬を市販している．

■PTの偽陽性を除外するには

PTは刺激反応が生じることを常に念頭におかなければならない．光毒性反応もしかりである．そこで，これまでPTで薬疹を特定した報告がない薬剤や，文献を引用しても正常コントロールのPTの報告がない薬剤については，個々の症例において，PTの反応がアレルギー反応か刺激反応か検討し，再現と希釈系列による最低惹起濃度を決定しておくことが重要である．もし刺激反応が否定できない場合は，少なくとも3名，できれば10名程度の正常コントロールのPTを行う必要がある．これらの検討によって，はじめてアレルギー反応と判定することができる．そして，このデータを集積して広く共有できるものにしていくことが重要と考えている．

■PTが陰性の場合に考えること

代謝物がアレルゲンであるなら，皮膚に貼っても陽性にはならない．感作の程度はさまざまであり，all or nothingではない．その反応は個体の免疫の状態，ウイルス感染や運動などに左右される．また免疫の状態によっては，PTが無反応の時期があるので，PTが陰性であっても，時期をずらして再度PTすることも無意味ではない．固定薬疹ではよく知られているが，皮疹のない部位では反応は出ない．必ず皮疹のあった部位へPTしよう．

■PTは安全か?

PTで感作する可能性もあるので，薬剤PTの濃度は最低惹起濃度で貼布する必要がある．このためにもデータの集積が必要である．

2. 薬疹と眼障害

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はじめに

Stevens-Johnson症候群(SJ症候群)と中毒性表皮壊死融解症 toxic epidermal necrolysis (TEN)はいずれも重症薬疹であり，皮膚のみでなく眼表面を含む全身の粘膜にも水疱やびらんを生じる．いずれも数週間で病変が消退するself-limiting diseaseであるが，急性期の眼傷害は角膜穿孔や角膜感染症など重篤な眼合併症を招き，生涯にわたる視力障害をもたらす．また全身および眼局所の炎症が沈静化しても，しばしば瞼球癒着や角膜混濁などの瘢痕性変化を生じ，視力障害とドライアイが慢性期(瘢痕期)の症状として持続する．

両疾患は致死的なことがあり得ることから発症時には全身管理が主体となるが，救命できた患者を長く苦しめるのは眼障害である．発症と同時に眼局所にも病変を生じていることが多く，眼合併症を可能な限り少なくするには，きわめて早期より眼科治療を開始することが必要である．

I. 急性期障害

1. 眼所見

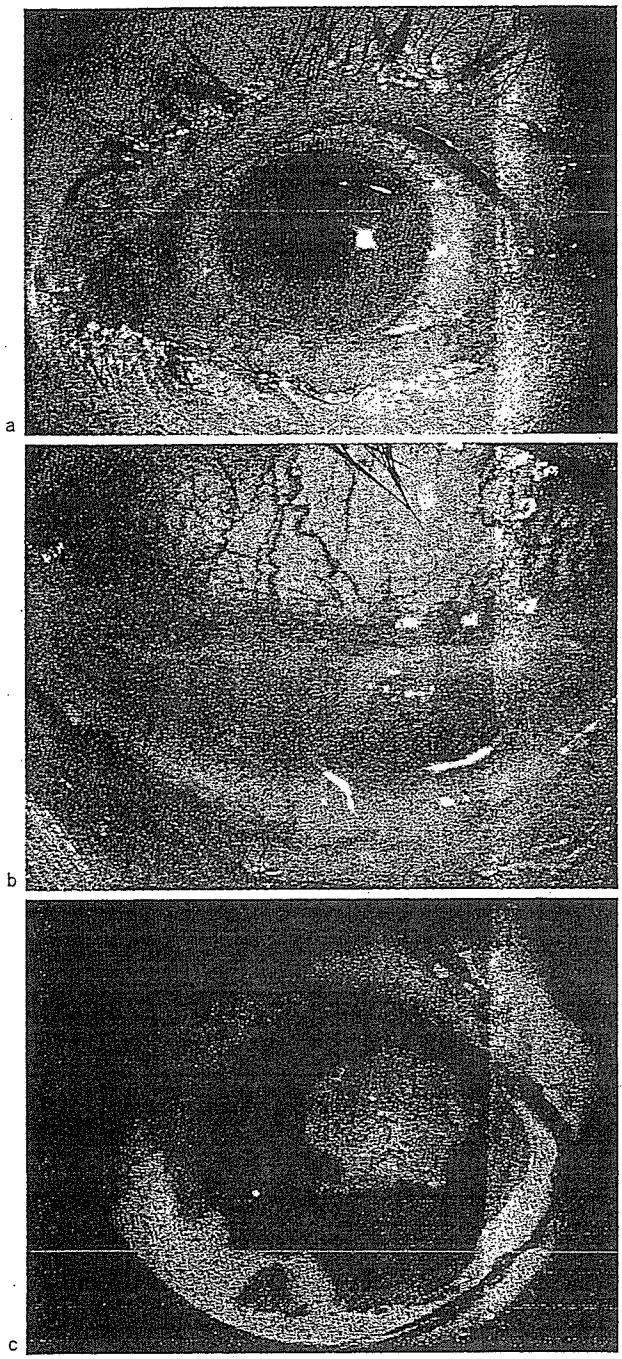
皮膚ならびに他の部位の粘膜病変とほぼ同時に，あるいは皮膚病変より半日ないし1日程度先行して急性結膜炎を生じる．具体的には結膜全体に及ぶ充血，眼瞼の発赤腫脹，眼脂がみられ，最も炎症の強い時期には，偽膜形成と角結膜上皮欠損(重症では全角膜上皮欠損)を伴う(図1)．重症では眼瞼腫脹および瞼球癒着により開瞼すらできない状態となる．眼瞼の高度な炎症により，睫毛が脱落する．

2. 何が生じているのか?

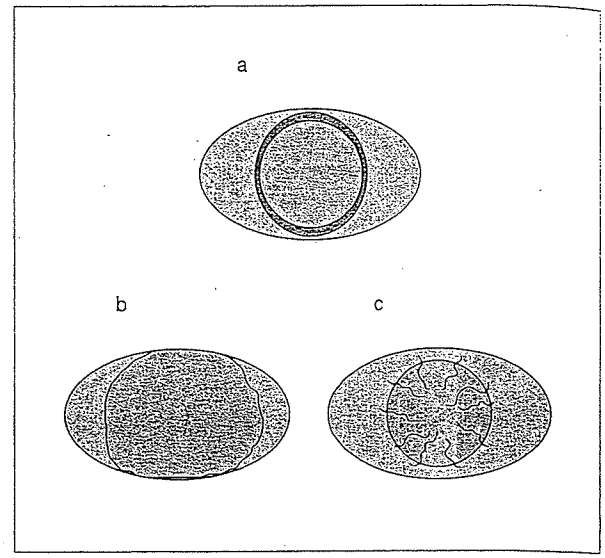
偽膜はフィブリン，壊死を生じた上皮細胞，浸潤細胞(主に好中球)からなり，眼表面の炎症が高度であることを示す．眼表面上皮(角膜上皮および結膜上皮)は免疫的に攻撃され，軽症では点状の角膜上皮障害，中等症以上では角膜上皮欠損や結膜上皮欠損，あるいは広範囲な角結膜上皮欠損を生ずる．言い換えると急性期には，「眼瞼を含む眼表面全体が免疫的に攻撃され，高度な炎症と上皮障害を生じる」．この免疫異常の詳細については未だ解明されていない．

3. 角膜上皮幹細胞の消失と視力予後

角膜上皮の幹細胞は，角膜を取り囲む幅1～2 mmの帯状部分(角膜輪部と呼ばれる)に基底細胞の一部として存在すると考えられており，この角膜上皮幹細胞は正常時にはあまり分裂していないが，ひとたび角膜に障害が生じると速やかに分裂・増殖を繰り返し大量の角膜上皮細胞を再生する[1]．急性期に輪部を含む上皮欠損を生じ，角膜上皮幹細胞(輪部上皮細胞)が消失すると，上皮欠損部は角膜上皮により修復できず周囲から伸展する結膜組織で被覆される．結膜組織は上皮のみでなく結合組織を伴って侵入するために，角膜は厚い不透明組織で覆われて表層性の角膜混濁と血管侵入をきたす(図2, 4, 5a)．一方，角膜上皮欠損



[図1] 急性期の眼所見(同一症例)
a 急性結膜炎
Stevens-Johnson 症候群の発症後5日．結膜充血，眼瞼腫脹，眼脂を認める．
b 偽膜形成
発症後2週．眼瞼に白色の膜様物(偽膜)を認める．
c 角膜上皮欠損
偽膜形成と同時期に角膜中央やや上側にほぼ円形の上皮欠損を生じ(緑色部分)，球結膜および眼瞼結膜にも広範囲の上皮欠損を生じた．



[図2] 幹細胞の消失と予後
正常眼において角膜上皮幹細胞は，角膜を取り囲む幅1～2mmの輪部と呼ばれる帯状部分(紫色部)に存在する(a)．SJ症候群・TENの急性期に広範囲の上皮欠損(緑色部分)を生じて輪部上皮が消失すると(b)，角膜は血管や結合組織を伴う結膜組織で被覆される(c)．

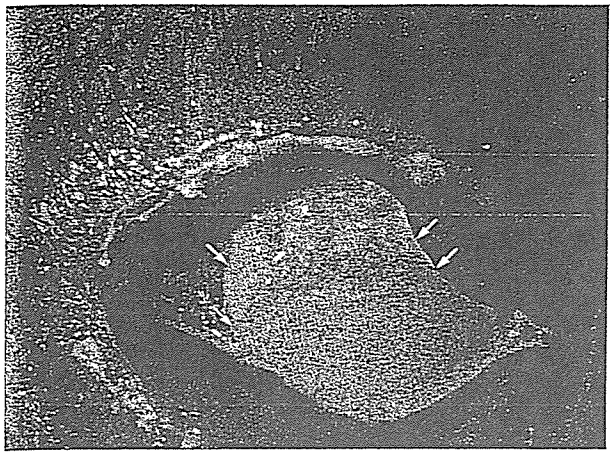
を生じても角膜上皮幹細胞が残存した場合には，上皮欠損は角膜上皮により修復され，ほぼ透明化する．このように，角膜周辺部に存在する角膜上皮幹細胞が消失するか否か，その後の角膜の透明性に大きく影響する．角膜上皮幹細胞の存在をみるには，palisades of Vogtと呼ばれる皺状構造が良い臨床指標である．

4. さらなる合併症

角膜上皮幹細胞が傷害されると上皮修復が困難となり，しばしば遷延性上皮欠損に陥る(図3)．遷延性上皮欠損は角膜感染症，角膜融解，角膜穿孔などを生じやすく，重篤な視力障害を後遺症としてもたらす．角膜上皮が広範囲に欠損しているときは医学的にはハイリスクであっても視力は比較的良好であり，患者の視力は重症度の指標とはなりえない．

5. 急性期の治療

眼表面の炎症，瞼球癒着を抑えて眼表面上皮を温存することと，眼表面の2次感染防止に努めることが重要である(表1)．眼表面における炎症の



[図3] 遷延性上皮欠損
Stevens-Johnson 症候群の急性期に広範囲に角結膜上皮欠損(全角膜上皮欠損＋結膜上皮欠損)を生じ，角膜上皮幹細胞が全周性に消失した．写真は発症後2ヵ月であるが遷延性上皮欠損(矢印，緑色部分)となっており，このような上皮欠損はきわめて難治である．

[表1] 各時期の眼所見と治療

	眼所見	治療・処置
急性期	眼表面の上皮欠損(角膜・結膜)	眼表面の炎症を制御(ステロイド全身・局所投与) 上皮を保護(治療用 SCL*1 装用，眼軟膏など)
	眼脂	抗菌薬の局所投与
	偽膜形成	偽膜除去
	瞼球癒着	癒着解除
慢性期(瘢痕期)	ドライアイ	人工涙液の点眼，涙点プラグ，涙点縫合術
	睫毛乱生	睫毛抜去
	瞼球癒着	(羊膜移植，培養口腔粘膜上皮移植)*2
	角膜混濁	(輪部移植，培養角膜上皮移植，培養口腔粘膜上皮移植)*2

*1 SCL：ソフトコンタクトレンズ
*2 慢性期障害に対するこれらの手術治療は一部の機関でのみ可能

程度，上皮欠損の範囲を把握し，治療方針を立てる．所見は日々刻々と変化するが，その推移と治療効果をみながら，さらなる治療を進める．

1) 眼表面の消炎

ステロイドの大量全身投与に加えて，局所にもステロイドを投与する．ただし感染症発症を招くおそれがあるため，患者と家族に感染症発症のリスクと本症の視力予後について十分に説明したうえで，抗菌薬を併用しながらステロイドを投与する．具体的にはベタメタゾンの点眼(1日4回程度)が消炎のために効果的であり，炎症が高度な場合にはベタメタゾン眼軟膏を併用する．全身所見の軽減とともに眼所見の改善を得ることができれば，ゆっくりと局所ステロイド量を減量する．

2) 感染症予防

患者は眼表面にMRSA(methicillin-resistant *Staphylococcus aureus*)を保菌しやすい．初診時に結膜嚢培養あるいは分泌物の塗抹および培養検査を行い，その後は週1回程度の検査を継続する．菌を検出すれば薬剤感受性を考慮して，抗菌薬を局所投与する．患者がMRSAを保菌しやすい原因はわかっていないが，ICUでの治療との関係は否定できない．

3) 偽膜除去と癒着解除

現在のところ，偽膜は除去するのが好ましいという意見が多数を占める．生じた偽膜はていねいに除去する．偽膜除去の操作が炎症を惹起してはならず，清潔な綿棒に絡め取るように除去するとよい．急性期に生じる瞼球癒着を放置すると強固な器質的癒着となる．点眼麻酔下に硝子棒を用いて機械的に癒着を剝離し，消炎に努める．

6. 急性期の眼傷害が遷延するとき

通常3～4週間程度で皮膚症状が落ち着いてくるが，眼の炎症所見が依然続いて角膜上皮欠損が遷延することがある(図3)．あるいは，皮膚症状が軽快したためにステロイドの全身投与量を減らしたあと，眼炎症所見が再燃することがある．充血，角膜びらんなどの炎症所見が続く場合には，眼表面の消炎を目的として，ステロイドの全身，局所投与を引き続いて行う．

ただしステロイドの副作用として眼圧が上昇することに注意を払わねばならず，漫然としたステロイド投与は避けなければならない．投薬の効果を得られず，遷延化した眼の炎症をコントロールできないときは，治療経験のある医師あるいは角膜専門医などに相談することが望ましい．

II. 慢性期障害

1. 眼所見

1) 瘢痕性角膜混濁

結膜上皮が血管・結合織を伴って角膜表面を被覆すると，角膜表面は不透明，凹凸不整となり，著しい視力障害をきたす．眼表面を被覆した結膜上皮は分化異常をきたし，重症では眼表面が皮膚のように角化する(図4)．

2) 眼瞼の異常

炎症の後遺症として睫毛乱生，瞼球癒着などが生ずる．

3) ドライアイ

正常の涙液は油層，水層，粘液層の3層からなり，油層はマイボーム腺，水層は涙腺，粘液層は結膜杯細胞と眼表面上皮から成分を供給される．慢性期患者の多くは，結膜の杯細胞消失によるムチン分泌不全，涙腺導管の閉塞による涙液分泌不全を伴う．さらにはマイボーム腺の腺構造が消失し，涙液減少型ドライアイに加えて蒸発亢進型ドライアイを合併する．

4) 結膜充血

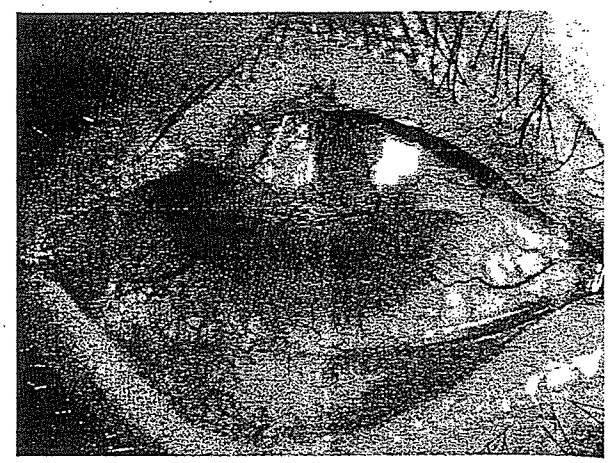
慢性期には眼表面の状態は落ち着くが，組織学的には非特異的な炎症が存在する[2]．一部の症例では軽度の再燃を繰り返しながら病変が進行する．

2. 症状

角膜混濁による視力不良のほか，乾燥感，異物感，羞明，眼痛などが慢性期の症状として持続する．

3. 慢性期の治療

眼表面の管理が治療の主体となる．ドライアイ，睫毛乱生に対する治療を細やかに行うことが必要であり，これらを放置すると眼表面の炎症，感染症，遷延性上皮欠損などを生じて瘢痕性変化をさらに進行させる可能性がある．定期的な経過観察を行い，睫毛抜去，ドライアイ治療(人工涙液の点眼，涙点プラグなど)を行う．易感染性の



[図4] 慢性期の眼所見
上眼瞼と角膜の癒着(瞼球癒着)がある．角膜は表層性に強く混濁し，血管侵入を伴う．視力は眼前手動弁である．

傾向があり，眼脂を伴って充血を生じた場合には，結膜嚢培養を行い，抗菌薬を点眼する．

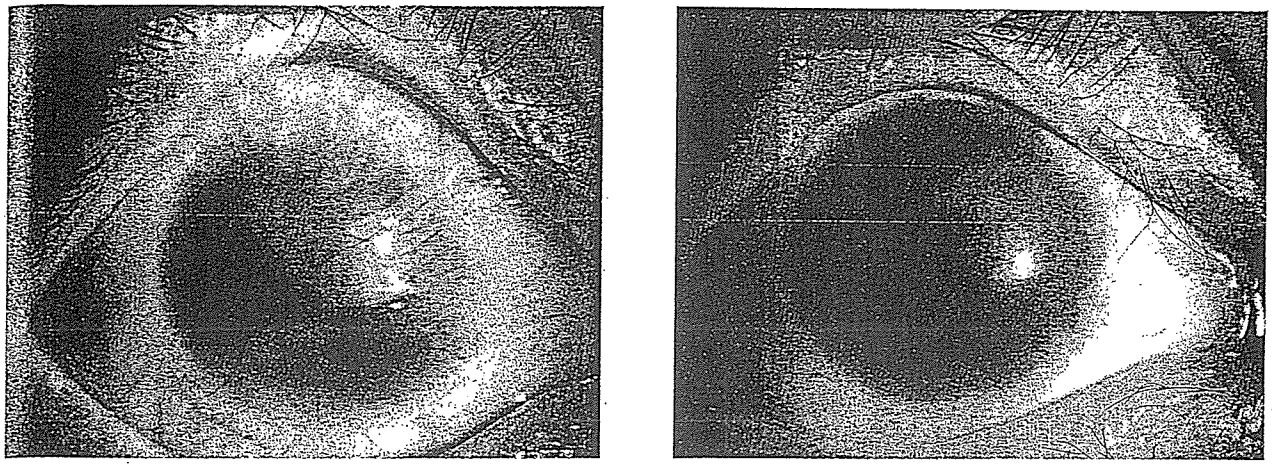
慢性期に軽度の炎症が持続，あるいは再燃を繰り返す症例がある．低濃度のステロイド点眼により炎症を抑制することは，瘢痕性変化の進行防止に有用と考えられている．

III. 手術治療の最前線

SJ症候群およびTENに対する角膜移植手術は，術後に著明な炎症を生じて予後不良であるために長く禁忌とされてきた．しかし近年では羊膜移植併用などにより瘢痕組織の除去，癒着解除と角膜上皮移植(輪部移植など)がなされるようになってきた．

筆者らの施設では，輪部幹細胞を含む角膜上皮を分離して羊膜上に培養し，生体の角膜上皮と同様に多層化した上皮(培養角膜上皮)を作成する方法を用いて，1999年以降SJ症候群を含む難治性疾患を対象に培養角膜上皮移植を行ってきた[3,4]．さらに2002年以降，患者本人の細胞を用いて口腔粘膜上皮シートを作成し，培養口腔粘膜上皮移植を行っている[5]．

薬疹に合併した急性期の遷延性上皮欠損は上述したようにハイリスクであるが，これまで有効な治療方法がなかった．しかし培養角膜上皮移植あ



[図5] 培養角膜上皮移植例
角膜表面に全周より結膜組織が侵入し，術前視力は0.08であった．
表層の瘢痕組織を切除，培養角膜上皮移植を施行し，術後視力0.8を得た．
a 移植前，b 移植後

るいは培養口腔粘膜上皮移植の術後には，速やかな上皮化と消炎を得ることが可能であり，その後の瘢痕形成も少ない．また瘢痕性混濁に至った慢性期症例に対し，培養角膜上皮移植が視機能の回復という面で成果をあげている(図5)．培養口腔粘膜上皮移植は，透明性の面で培養角膜上皮移植よりやや劣るが，自家移植であることから拒絶反応のリスクがなく術後投薬が少なくてすみ，小児や高齢者に有用である．

おわりに

どの科の医師であってもSJ症候群，TENに遭遇する可能性をもつが，視力予後が不良であること，全身治療に加えて発症早期からの眼科治療が必要であることは意外に知られていない．全身状態が重篤であるほど眼には関心がいきにくいが，初期より眼科医を含む医療チームが治療にあたることが望ましい．

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Vaccination and infection as causative factors in Japanese patients with Rasmussen syndrome: Molecular mimicry and HLA class I

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Abstract

Rasmussen syndrome is an intractable epilepsy with a putative causal relation with cellular and humoral autoimmunity. Almost half of the patients have some preceding causative factors, with infections found in 38.2%, vaccinations in 5.9% and head trauma in 8.9% of Japanese patients. In a patient with seizure onset after influenza A infections, cross-reaction of the patient's lymphocytes with GluRε2 and influenza vaccine components was demonstrated by lymphocyte stimulation test. Database analyses revealed that influenza A virus hemagglutinin and GluRε2 molecules contain peptides with the patient's HLA class I binding motif (HLA − A*0201). The relative risks of HLA class I genotypes for Rasmussen syndrome are 6.1 (A*2402), 6.4 (A*0201), 6.3 (A*2601) and 11.4 (B*4601). The relative risks of HLA class I-A and B haplotypes are infinity (A*2601 + B*5401), 21.1 (A*2402 + B*1501), 13.3 (A*2402 + B*4801) and 5.1 (A*2402 + B*5201). Some alleles and haplotypes of HLA class I may be the risk factors in Japanese patients. Cross-reactivity of cytotoxic T lymphocytes may contribute to the processes leading from infection to the involvement of CNS.

Keywords: *Rasmussen syndrome, HLA, cytotoxic T cells, influenza, vaccination, epilepsy*

Introduction

Rasmussen's encephalitis is a slowly progressive, autoimmune-mediated chronic inflammatory disease of the CNS. The mean age of onset is 7.4 years. The disease may be preceded by some causative factors including infection, and the initial seizure episode manifests various forms such as partial onset generalized tonic-clinic (pGTC) seizures (30%), focal motor seizures (26%) and complex partial seizures (CPS) (26%) (Andermann 1991). One third of the patients have preceding infections within 1 month before onset. Patients with typical Rasmussen's encephalitis manifest frequent intractable partial motor seizures in the acute phase, characteristically epilepsia partialis continua (EPC) (56%). Patients begin to manifest EPC 1.8 years after the onset of epilepsy, but the seizure frequency decreases markedly in the residual stage (Andermann 1991, Bien et al. 2002b) (Figure 1). Patients in the residual stage are affected by hemiplegia (96%), mental deterioration (85%), visual field defect (49%), and cortical sensory defect (29%) (Andermann 1991). Histological examination reveals infiltration of T lymphocytes and microglia cells, astrocytosis, and neuronal loss in the lesion (Aguilar and Rasmussen 1960, Andermann 1991, Farrell et al. 1995). Functional hemispherectomy is the only reliable therapy when the non-dominant side is involved, but hemiparesis and hemianopsia are

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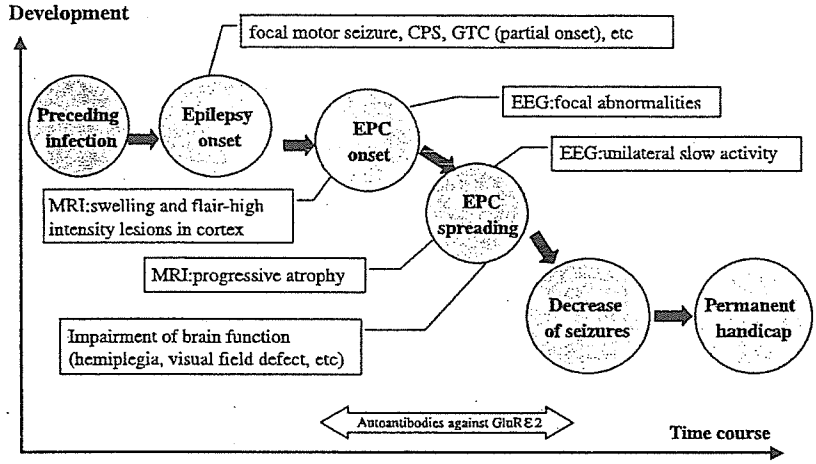

Figure 1. Schematic presentation of the typical clinical course of Rasmussen syndrome. After preceding infections, epileptic seizures (focal motor seizures or partial onset generalized tonic clonic convulsions, etc.) appear, followed by progressive deterioration of clinical symptoms and aggravation of EEGs and MRI abnormalities. In the residual stage, permanent handicap is observed, but epileptic seizures decrease. GTC, generalized tonic clonic seizure; GluR, glutamate receptor; EPC, epilepsia partialis continua.

unavoidable after operation. When the dominant side is affected, there is no effective therapy.

Viral infections were implicated as the causal agent of Rasmussen's encephalitis in early investigations (Andermann 1991), and direct infection by several candidate viruses (CMV, tick-borne encephalitis virus, etc.) has been postulated as one of the possible mechanisms causing the disease (Takahashi 2006) (Figure 2).

Rogers et al. (1994) reported glutamate receptor 3 (GluR3) as an autoantigen in Rasmussen's encephalitis, and proposed autoantibodies against this molecule to be one cause of Rasmussen's encephalitis (humoral autoimmune hypothesis). Their report

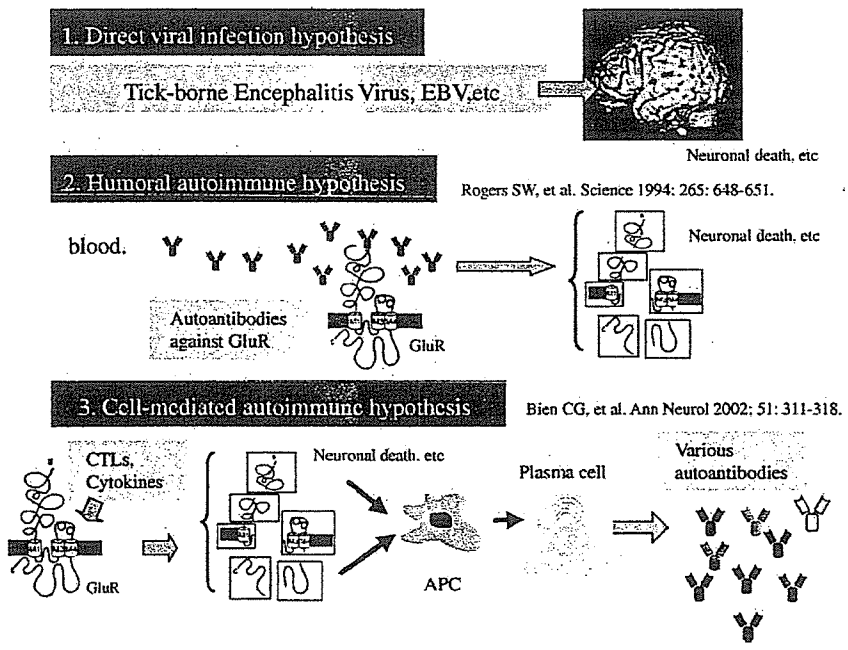

Figure 2. Hypotheses of autoimmune pathologies in Rasmussen syndrome. Direct viral infection hypothesis presumes that viral particles invade the brain and cause neuronal death, etc. Humoral autoimmune hypothesis supposes that autoantibodies against neural molecules (GluR3, etc.) play the primary roles to develop Rasmussen syndrome. Cell-mediated autoimmune hypothesis speculates that CTLs and/or cytokines from $CD4^{+}$T cells play the primary roles. EBV, Ebstein bar virus; GluR, glutamate receptor; APC, antigen-presenting cells.

introduced a new perspective of autoimmune-mediated mechanism to the field of epilepsy. Several pathological roles of autoantibodies against GluR3 have been demonstrated, including excitotoxicity (Levite and Hermelin 1999), complement-dependent cell death (He et al. 1998) and membrane attack complex (MAC) (Xiong and McNamara 2002, Xiong et al. 2003) have been shown, although induction of currents through GluR remains controversial (Twyman et al. 1995, Watson et al. 2004). The MAC is composed of several complements, and appears to induce functional pore in cell membrane, leading to depolarization and osmotic lysis of neurons. These data indicate that autoantibodies can directly cause impairment of neural functions.

On the other hand, Bien et al. (2002a) proposed the destruction of neurons by cytotoxic T cells (CTLs) as a new pathogenic mechanism in Rasmussen's encephalitis (cell-mediated autoimmune hypothesis). Lymphocytic infiltration containing predominantly T cells and sparsely B cells can be observed in surgically resected tissues from patients with Rasmussen's encephalitis (Farrell et al. 1995), and local CNS immune responses in Rasmussen's encephalitis include clonal expansion of T cells responding to discrete antigen epitopes (Li et al. 1997). Peripheral blood lymphocytes from patients are sensitized to GluRε2 (Takahashi et al. 2005). Heterogeneous autoantibodies against neuronal molecules (including GluR3, GluRε2, neuronal acetylcholine receptor alpha7, and munc-18) (Yang et al. 2000, Watson et al. 2001, Takahashi et al. 2003) and glial cells (Roubertie et al. 2005) are detected in Rasmussen syndrome. Autoantibodies against GluRε2 have epitopes predominantly in intracellular domains, and show epitope spreading evolutionally (Takahashi et al. 2003). We postulated that the autoimmune-mediated mechanism for the development of Rasmussen syndrome involves primarily cellular autoimmunity mediated by cytotoxic T cells, and evolutionarily involves humoral autoimmunity mediated by auto-antibodies (Takahashi et al. 2003, 2005). These autoimmune mechanisms of epileptogenesis after infections can be classified as parainfectious mechanisms (Figure 3) (Takahashi 2006).

Causative factors of in patients with Rasmussen syndrome

In our epilepsy center, 44% of Japanese patients with Rasmussen syndrome had prior infections or vaccinations, and approximately 8% had head trauma as preceding causative factors, and the frequencies are almost same in patients with EPC and in those without EPC (Table I) (Takahashi 2006). The microbes causing infections were not identified in the majority of patients, except in three patients infected by influenza virus and one patient by mycoplasma. Likewise, in the study conducted at Montreal Neurological Institute, the causative microbes were not documented except measles (encephalitis) and varicella (Andermann 1991).

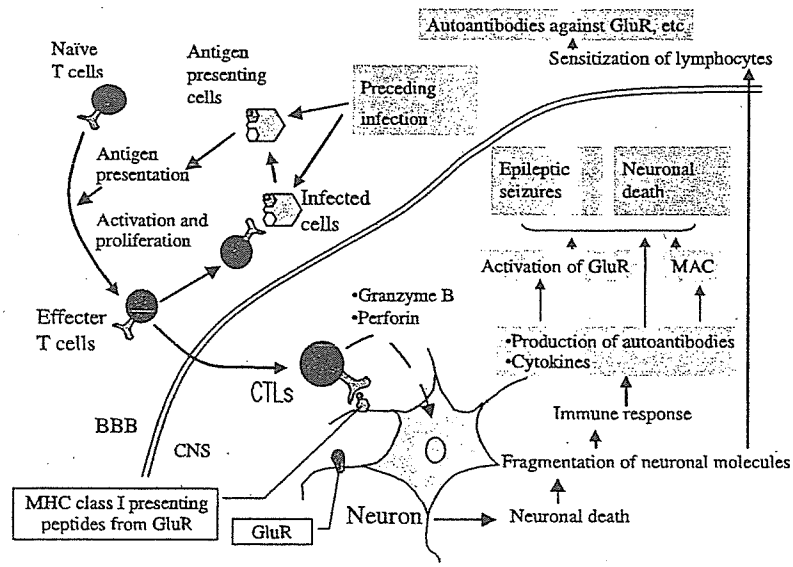

Figure 3. Involvements of CTLs and autoantibodies in the hypothetic mechanisms of the development of Rasmussen syndrome. Effecter T cells activated by preceding infections or vaccinations reach the CNS by crossing blood brain barrier, and cross-react with neurons, etc. resulting in apoptosis. Neuronal death leads to production of autoantibodies against CNS molecules and cytokines, which might contribute to the further neuronal death or epileptogenesis. Fragmented neuronal molecules reach systemic circulation and sensitize lymphocytes, resulting in production of autoantibodies in the blood. BBB, blood brain barrier; CNS, central nervous system; CTLs, cytotoxic T cells; GluR, glutamate receptor; MAC, membrane attack complex.

Table I. Causative factors in 34 patients with Rasmussen syndrome.

	EPC type	Non-EPC type	Total
Age of onset	6.3 ± 5.6	8.7 ± 8.0	7.4 ± 6.7
Preceding infections	8 (40.0%)	5 (35.7%)	13 (38.2%)
Fever only	4	1	5
Upper respiratory infection	2	1	3
Influenza	1	2	3
Mycoplasma	0	1	1
Aseptic meningitis	1	0	1
Vaccination	1 (5.0%)	1 (7.1%)	2 (5.9%)
Head trauma	2 (10.0%)	1 (7.1%)	3 (8.8%)
None	9 (45.0%)	7(50.0%)	16(47.1%)
Total	20	14	34

Therefore, it remains unknown whether specific microbes are involved in the development of Rasmussen syndrome. The contribution of molecular mimicry between microbial and neuronal molecules and degeneracy of T cell receptor recognition to the development of Rasmussen syndrome (autoimmune-mediated epilepsies) will be discussed later.

We encountered two patients who developed Rasmussen syndrome after vaccination, although vaccination was not reported as a causative factor in the series of Montreal Neurological Institute. One patient had EPC type Rasmussen syndrome. This patient received Japanese encephalitis vaccination at the age of 15 years. Two months after vaccination, he had the initial epileptic seizure, and subsequently evolved to intractable and frequent complex partial seizures (CPSs) and EPC. MRI lesions in left frontal lobe and autoantibodies against GluRε2 were detected. Focal resection of the left frontal lobe failed to control epileptic seizures, psychiatric symptoms and deterioration. Another patient had non-EPC type Rasmussen syndrome. This patient received measles–mumps–rubella triple vaccine at the age of 1 year. Three weeks later, he was affected by aseptic meningitis caused by the vaccination. He had intractable epileptic seizures from the age of two, and psychiatric symptoms (including anxiety) evolved subsequently. At the age of 14 years, right frontal lobectomy was conducted and successfully controlled the seizures.

Head trauma also was not reported as a causative factor in the patients of Montreal Neurological Institute, but we identified three patients with Rasmussen syndrome possibly related to preceding head trauma. As we sometimes experience patients with aseptic meningitis after head trauma, head trauma may facilitate the invasion of inflammatory T cells into the CNS. In patients with post-concussion syndrome after mild head injury, focal cortical dysfunction may occur in conjunction with the disruption of the blood brain barrier (Korn et al. 2005).

In the following sections, infection as a causative factor in Rasmussen syndrome will be illustrated using a specific case in which Rasmussen syndrome developed after influenza infection, especially focusing on the roles of molecular mimicry and HLA class I.

A case of Rasmussen syndrome after influenza A infection, and cross-reaction of lymphocytes

This patient, a boy, was 8 year-old at the time of this report (Case 1). His family history was unremarkable, with ovarian cyst in his mother and parkinsonism in his maternal grandfather. At the age of 3 years and 11 months, he had febrile generalized convulsion following an episode of influenza A infection that was confirmed by antigen detection from a nasal sample. Before the influenza infection, he had no neurological symptoms and no other preceding conditions that might precipitate the convulsions. Soon after the initial convulsion, at age 4, he had febrile convulsive status of left extremities associated with repeated influenza A infection. CSF was normal, and CT revealed no abnormalities. At the age of 4 years and 1 month, afebrile convulsive status appeared and phenobarbital (50 mg) was prescribed. Thereafter, his seizures became progressively intractable, in spite of a combination of several antiepileptic drugs (carbamazepine, zonisamide, valproic acid and phenytoin). At the age of 5 years and 4 months, EPC appeared after phenytoin was stopped abruptly and clobazam was added. He was referred to our epilepsy center for the treatment of Rasmussen syndrome at the age of 5 years and 5 months. He had hemiparesis of left extremities, EPC of left lower extremity, and several partial seizures in a day (Figure 4). After functional hemispherectomy, seizures were controlled completely. At age eight, he walked to school and attended a normal elementary school.

At presentation, IgG-autoantibodies against GluRε2 were detected in serum and CSF samples (Takahashi et al. 2003), but IgM-autoantibody was negative. The stimulation index obtained in the lymphocyte stimulation test (LST) stimulated with homogenates containing GluRε2 (^{3}H-thymidine

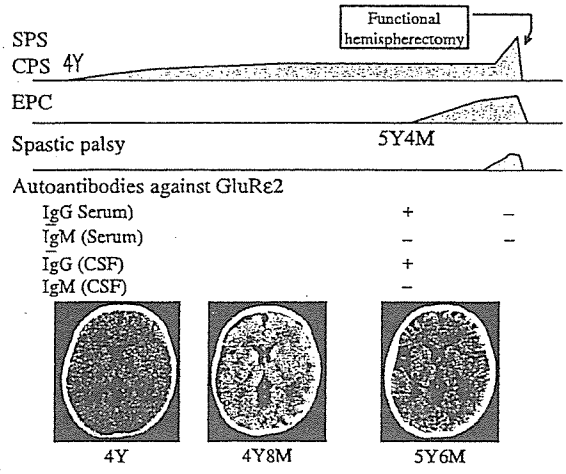

Figure 4. Clinical course of Case 1. Epilepsy occurred at the age of four, and progressive atrophy of right hemisphere started at the age of 5 year and 6 months. IgG-autoantibodies against GluRε2 were positive on admission, but became negative after functional hemispherectomy that successfully controlled seizures. SPS, simple partial seizure; CPS, complex partial seizure; EPC, epilepsia partialis continua.

uptake with stimulation/control ^{3}H-thymidine uptake) was 2.78 (Takahashi et al. 2005), and was higher than normal controls (0.63, 1.67) tested simultaneously (Figure 5). When LST was conducted by co-stimulation with homogenates containing GluRε2 and influenza vaccine, the stimulation index was 9.19 in this patient (Case 1 in Figure 5), and was

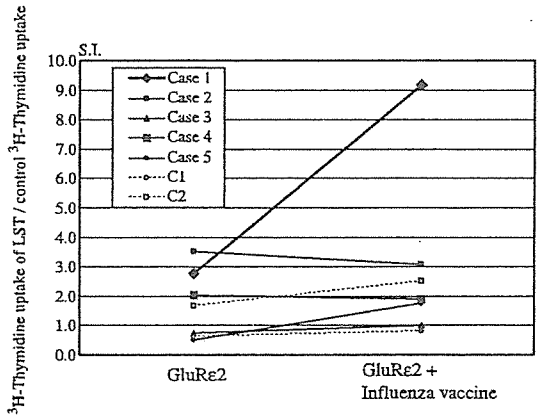

Figure 5. Stimulation index in lymphocyte stimulation test. Data on the left show stimulation indices (SI) (^{3}H-thymidine uptake with stimulation/control ^{3}H-thymidine uptake) obtained in lymphocyte stimulation test (LST) stimulated with homogenate containing GluRε2 (Takahashi et al. 2005). Data on the right show SI when LST was conducted by co-stimulation with homogenates containing GluRε2 and influenza vaccine. Case 1 is the case presented in the text, with influenza A infection as a causative factor. Case 2 is Rasmussen syndrome with no causal relationship with influenza. Cases 3–5 are epileptic cases (no Rasmussen syndrome) with autoantibodies against GluRε2. C1 and C2 are normal controls.

higher compared with other patients with Rasmussen syndrome or other epilepsies not related to preceding influenza infection (Cases 2–5). A synergistic increase in stimulation index with co-stimulation (GluRε2 + influenza vaccine) compared to GluRε2 stimulation alone was observed only in the present case. These data suggest that the lymphocytes of this patient are sensitized not only by influenza antigen but also by GluRε2, and that the T cell receptors of this patient can cross-react with peptides from influenza and GluRε2.

After the T cell receptors on CTLs recognize both the HLA class I molecule and its binding peptide expressed on antigen presenting cells (APCs), these CTLs are activated into cytotoxic effector cells that are capable of invading the CNS. If through molecular mimicry and T cell receptor redundancy, the CTLs activated by microbial peptides are able to recognize the HLA class I and binding peptide expressed on neurons, then the infection-activated CTLs may induce apoptosis of neurons. Therefore, HLA class I is one of the key molecules that determines autoimmune mechanisms underlying the process leading from infection or vaccination to Rasmussen syndrome.

HLA class I and theoretical cross-reaction of CTLs in Case 1

In the case presented above (Case 1), HLA genotyping identified HLA – A*0201, A*2402, and B*3501 (homo). HLA – A*0201 binds peptides with the following motif: [LM] – x(3) – V – x(2) – [VL] (x, free amino acid; L, leucine; M, methionine; V, valine). Database analyses (Genome Net: http://www.genome.jp/) revealed this motif in various viral molecules and neural molecules (Figure 6). If patients with HLA – A*0201 are infected by influenza A virus, the peptide *LAIMVAGL* from the hemagglutinin of influenza A is able to bind with A*0201 expressed on APCs. CTLs with T cell receptors that recognize A*0201 and the hemagglutinin peptide (influenza A) on APCs become activated and become effector CTLs. Theoretically, these effector CTLs can invade the CNS, and react with neurons expressing HLA – A*0201 and peptides containing the [LM] – x(3) – V – x(2) – [VL] motif, due to molecular mimicry and degeneracy of T cell receptor recognition (Uemura et al. 2003). Peptides having the HLA – A*0202 binding motif are found in various neuronal molecules, such as GluRε2 (*LVLAVLAV*, *MLLIVSAV*) and GluRε1 (*LPLDVNVV*). Therefore, we hypothesize that CTLs activated by influenza may cross-react with neurons that express GluRε2 under specific conditions such as the presence of costimulators. This hypothetic cross-reaction based on molecular mimicry of HLA-binding motif is compatible with our data of

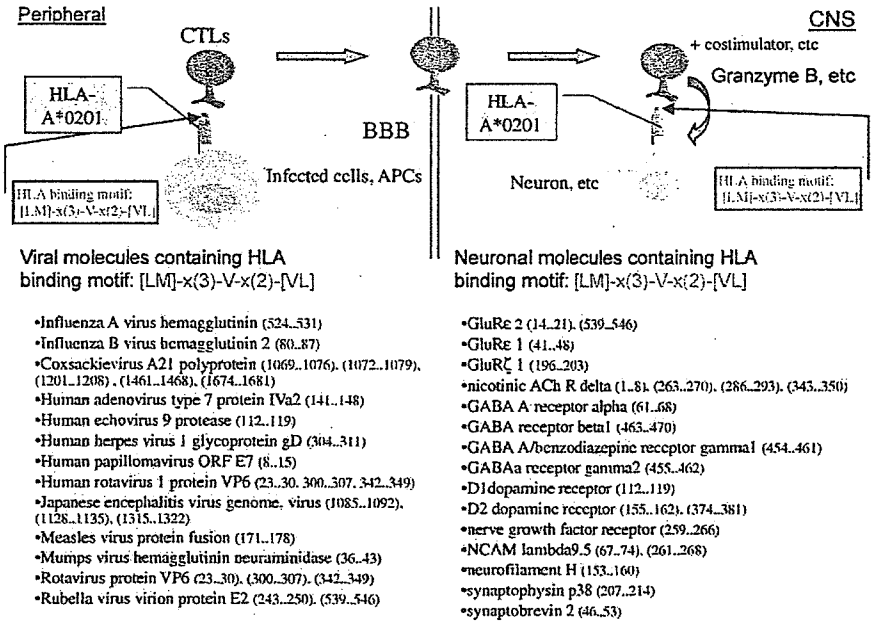

Figure 6. Viral and neural molecules containing specific binding motif for HLA − A*0201. Viral infection of host cells leads to expression of some parts of the viral peptides by binding with HLA class I molecule on the infected cells. CTLs expressing T cell receptors that recognize the peptide and HLA class I are activated, resulting in generation of effecter T cells. In individuals with HLA − A*0201, the binding motif is [LM] − *x*(3) − V − *x*(2) − [VL] (*x*, free amino acid; L, leucine; M, methionine; V, valine). Database analyses (Genome Net, http://www.genome.jp/) revealed many viral molecules containing this motif, as shown in the left column. The numbers in parentheses are sequence numbers indicating the sites of the motif. Effecter T cells are able to cross the blood brain barrier to reach the CNS, and theoretically can cross-react with neurons expressing the same motif on HLA class I, under specific conditions such as the presence of costimulator. Database analyses revealed many neural molecules including NMDA-GluRs, which contain the motif, as shown in the right column.

lymphocyte cross-reactivity between GluRε2 and influenza vaccine observed in Case 1 (Figure 5). Since CTLs activated by influenza can react with a broad spectrum of neuronal molecules, theoretically, apoptotic lesions caused by CTLs may distribute widely in the brain. On the other hand, possible interactions of the activated CTLs of Case 1 with a variety of microbial molecules (Figure 6) may explain the symptomatic aggravation triggered by infections other than influenza after the onset of Rasmussen syndrome. T cell clones from type 1 diabetes patients have been shown to react with several kinds of microbial mimicry peptides (Uemura et al. 2003). Similar molecular mimicry may also exists for HLA − A*2402 and B*3501. These molecules also have specific binding motifs. Database search identified diverse peptides containing these specific motifs in both microbial and neural molecules.

HLA class I in patients with Rasmussen syndrome

We studied the genotypes of HLA class I in 16 Japanese patients with Rasmussen syndrome (EPC type, 9; non-EPC type, 7) by PCR amplifications. The data were analyzed statistically using Chi-square for independence test. HLA − A*2402 is a popular genotype (36.5% of Japanese population) and was found in 77.8% of EPC type patients ($p = 0.016$). The frequencies of HLA − A*0201 and HLA − A*2601 were higher in non-EPC type patients (both 42.9%) than in Japanese population (10.7 and 11.3%, respectively) ($p = 0.033$ and 0.038, respectively). HLA − B*5201was found more frequently in EPC type patients (33.3%) than in Japanese population (10.9%) ($p = 0.070$), while HLA − B*4601 was more frequent in non-EPC type patients (28.6%) than in Japanese population (3.4%) ($p = 0.025$). The relative risks of various HLA class I genotypes for Rasmussen syndrome range from 6 to 11 (Table II), which are at the same levels as systemic lupus erythematosus (DR2) and acute anterior uveitis (B27) (Marsh et al. 2000). The relative risks of HLA class I-A and B haplotypes range from 5 to ∞. Since the haplotype of A*2601 + B*5401 was not observed in 561 Japanese subjects, the risk is infinity.

The HLA class I types that have higher relative risks may have a greater potential to induce cross-reactions of CTLs between microbes and neurons, and consequently may be found at higher frequencies in patients with Rasmussen syndrome. The binding motifs of these HLA class I types probably exist frequently in molecules from microbes commonly found in Japan and in molecules derived from neurons.

Table II. HLA class I genotypes and relative risks in patients with Rasmussen syndrome.

HLA genotypes	Clinical phenotype	Relative risk
HLA class I-A		
A*2402	EPC type	6.1
A*0201	Non-EPC type	6.4
A*2601	Non-EPC type	6.3
HLA class I-B		
B*4601	Non-EPC type	11.4
HLA − A + B haplotypes		
A*2402 + B*4801	EPC type	13.3
A*2402 + B*1501	EPC type	21.1
A*2402 + B*5201	EPC type	5.1
A*2601 + B*5401	Non-EPC type	∞

∞, infinity.

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Infections as causative factors of epilepsy

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Epilepsies bearing some relationship to infections or vaccinations are often encountered clinically. While the onset of epilepsy or aggravation of seizures may follow common infections or vaccinations, complete seizure control has also been observed after infections. However, the true mechanisms underlying the relationship between infections and epilepsies have not been fully elucidated. Recently, advances in immunology have contributed to the study of autoimmune mechanisms in Rasmussen's syndrome, a prototype of autoimmune epilepsy related to infections. The roles of autoimmunity, including cytotoxic T cells and autoantibodies against neural molecules, have been demonstrated in Rasmussen's syndrome. This review postulates the probable molecular mimicry of microbial and neural components in Rasmussen's syndrome and proposes possible autoimmune mechanisms related to the development of symptomatic epilepsies.

Epilepsy is a common neurological disease affecting 1–2% of the population and the onset of epilepsy is frequent in childhood. Childhood-onset epilepsy can begin after an infection episode, or even after vaccination, albeit rarely. Even after the onset of epilepsy, status epilepticus tends to occur under febrile conditions associated with infections or vaccinations. Parents of such pediatric patients usually suspect a causal relationship between the epilepsy (status epilepticus) and infection or vaccination. However, the question of how infections or vaccinations cause epilepsies remains largely unanswered. This review summarizes several proposed relations between infection (or vaccination) and epilepsy (Table 1) (Figure 1).

The etiologies of childhood epilepsy are classified into idiopathic (64%), prenatal (15%), perinatal (9%) and postnatal (12%) [1]. Infection of the CNS, a postnatal etiology, accounts for 4% of childhood epilepsies. In the author's epilepsy center, 12% of admitted cases of intractable partial epilepsy or generalized epilepsy were attributed to CNS infections (acute viral encephalitis, bacterial meningitis, etc.) [2]. These data suggest that CNS infections (direct infectious mechanisms) are an important cause of intractable epilepsies. Generally speaking, direct infectious mechanisms seem to include primary viral encephalitis, secondary autoimmune encephalitis and subacute sclerosing panencephalitis (Figure 1, routes 1, 2 and 4). While virus particles are found in CNS tissues in primary viral encephalitis, virus particles are absent in secondary autoimmune viral encephalitis. Strictly speaking, secondary autoimmune viral encephalitis is not classified as a direct virus infectious mechanism, but is included in parainfectious mechanisms.

Human herpes virus (HHV)-6 is an ubiquitous virus and causes exanthema subitum, a common disease in infants, and subsequently establishes latency in the CNS [3,4]. HHV-6 was detected in approximately 50% of the surgically resected brain tissues from patients with mesial temporal lobe epilepsy (mTLE), suggesting that reactivation of HHV-6 in astrocytes may have a role in the development of mTLE [5]. These latent infection and reactivation mechanisms may contribute to certain types of epilepsies (Figure 1, route 3).

Rasmussen's encephalitis is a slowly progressive disease of chronic inflammation in the CNS, resulting in hemiplegia (96%), mental deterioration (85%), visual field defects (49%) and cortical sensory defects (29%) [6]. Patients with typical Rasmussen's encephalitis manifest frequent intractable partial motor seizures in the acute phase, characteristically epilepsia partialis continua (EPC) (56%), but the frequencies of seizures decrease markedly in the residual stage [6,7]. Histological examination has revealed infiltration of T lymphocytes and microglia cells, astrocytosis and neuronal loss [6,8,9]. Although viral infection appeared to be causally related to Rasmussen's encephalitis in early investigations, Rogers and colleagues reported glutamate receptor (GluR)3 as an autoantigen in Rasmussen's encephalitis, which could be a cause of Rasmussen's encephalitis [10]. On the other hand, destruction of neurons by cytotoxic T lymphocytes (CTLs) was presented as a new

Keywords: autoantibodies, autoimmunity, cytotoxic T cell, epilepsy, glutamate receptor, HLA, infection, tacrolimus, vaccination

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Table 1. Proposed mechanisms underlying the development of epilepsies after infections and vaccinations.

Mechanisms	Method
Direct infection mechanisms	Microbes invade the CNS and directly cause insults resulting in epileptogenesis **(Figure 1, routes 1 and 2)**
Latent infection and reactivation mechanisms	Viruses remain latent in the CNS and reactivation of the viruses causes epilepsies **(Figure 1, route 3)**
Parainfectious mechanisms	Viruses infect tissues outside the CNS and affect the CNS through immunological mechanisms **(Figure 1, routes 4 and 5)**
Modification of synaptic transmission mechanism	Febrile seizures cause long-lasting modification of synaptic transmissions, resulting in epilepsy **(Figure 1, route 6)**
Triggering mechanisms	Fever associated with infections or vaccinations incidentally triggers the onset of fever-sensitive epilepsy **(Figure 1, route 7)**

pathogenic mechanism in Rasmussen's encephalitis by Bien and coworkers [11]. The author has suggested a mechanism by which initial cellular autoimmunity is evolutionally affected by humoral autoimmunity [12,13]. These autoimmune mechanisms of epileptogenesis following infections are considered to be parainfectious mechanisms (Figure 1, routes 4 and 5). An overview of the relationship between infections and autoimmunity in Rasmussen's syndrome will be discussed in this article.

Febrile seizures are the most common convulsive events in humans, and 4–5% of the population has at least one febrile seizure during their life time [14]. Complicated febrile seizures during early childhood or infancy seem to be related to the development of mTLE with mesial temporal sclerosis [15], although it still not clear if complex febrile seizures are an epiphenomenon or a causative factor [16]. Febrile seizures result in persistent modification of neuronal excitability in limbic circuits in the developing rat brain, which lasts into adulthood [17]. This modification of synaptic transmission mechanism in the hippocampus after febrile seizures induced by infections may contribute to the development of mTLE (Figure 1, route 6).

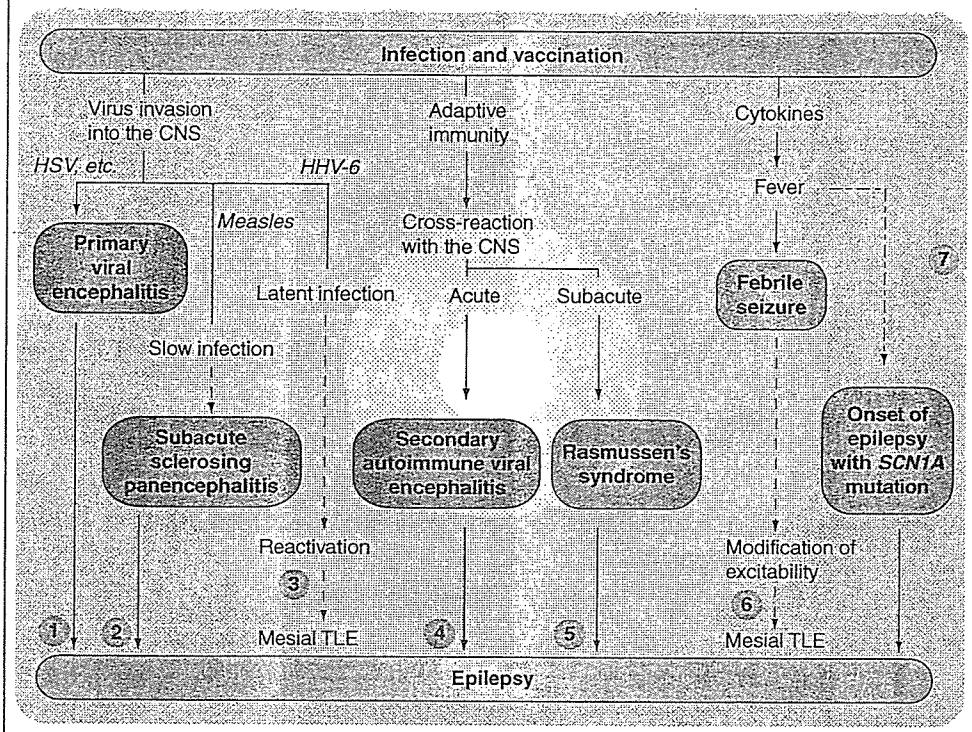
Recent advances in genetic molecular approaches have revealed several types of epilepsy related causally to gene mutations in patients with idiopathic etiologies [18]. Patients with sodium channel (SCN)1A mutations have frequent fever-induced seizures during common infections [19,20]. In patients with severe myoclonic epilepsy in infancy (SMEI), the onset of epilepsy usually follows fever-induced seizures associated with infections. In these patients, infections *per se* do not develop epilepsies but incidentally trigger the onset of epilepsies (Figure 1, route 7).

The relationship between vaccination and epilepsy is rarely documented, compared with the association between infections and epilepsies as described previously. Monitoring of post-vaccination adverse events for 8 years in Japan identified 269 patients manifesting neurological symptoms after diphtheria–tetanus–pertusis (DTP, 72 cases), measles (76 cases), rubella (20 cases), Japanese encephalitis (88 cases) or influenza vaccination (13 cases) [101]. These events include encephalitis (42 patients), convulsions (171 patients) and motor disturbance (5 patients). In these case reports, a causal relation with vaccination could not be denied, but confirmation of a definitive causality awaits future controlled studies. For DTP and mumps–measles–rubella (MMR) vaccinations, a transient increase in risk for febrile seizures has been reported, but not for afebrile seizures [21]. Analysis in the USA showed that inactivated influenza vaccination among children less than 2 years of age was safe, although two patients with first afebrile seizure after vaccination were reported [22]. Smallpox vaccination caused no neurological adverse events at rates above baseline estimates in the USA, although more than 20 serious adverse events were reported [23]. Owing to the small numbers of patients with neurological adverse events after vaccination, the causal relationship and hypothetic mechanisms underlying the development of epilepsy after vaccination have not been documented. However, the same mechanisms as infections might contribute to the development of epilepsy after vaccination (Figure 1). This review will focus on the frequency of vaccination as a possible causative factor of Rasmussen's syndrome.

Rasmussen's syndrome & causative factors (infections & vaccinations)

Rasmussen's syndrome is a prototype of epilepsy related causally to infections. In our epilepsy center, 38% of the patients have preceding infections, approximately 6% have vaccinations and 8.8% have head trauma as possible causative

Figure 1. Pathological routes leading from infections and vaccinations to the development of epilepsies.



Virus invasion of the CNS leads to direct infection mechanisms **(routes 1 and 2)** or reactivation of latent infection **(route 3)**. Adaptive immunity after infection or vaccination leads to parainfectious mechanisms **(routes 4 and 5)**. Cross-reacting T cells and autoantibodies against CNS molecules play an important role in parainfectious mechanisms. Febrile seizures cause long-lasting modification of synaptic transmissions, resulting in epilepsy **(route 6)**. Fever associated with infections or vaccinations incidentally triggers the onset of fever-sensitive epilepsy **(route 7)**.
HHV: Human herpes virus; HSV: Herpes simplex virus; SCN: Sodium channel; TLE: Temporal lobe epilepsy.

factors, and the frequencies are the same in patients with and without EPC (Table 2). Although vaccination was not reported as a causative factor in the study conducted at the Montreal Neurological Institute [6], two patients in the author's institute had Rasmussen's syndrome after vaccinations (Japanese encephalitis and MMR) [24]. CTLs activated by these infections or vaccinations may invade the CNS and cross-react with neurons expressing CNS molecules, resulting in neuronal apoptosis. Immunological studies are needed regarding cross-reactivity of patients' CTLs to confirm the definitive causal relationship between these possible causative factors (infections and vaccinations) and Rasmussen's syndrome [24]. Head trauma has also not been reported as a causative factor in patients of the Montreal Neurological Institute [6], but there are three patients who had a possible association with head trauma. As aseptic meningitis is sometimes observed after head trauma, this may facilitate the invasion of inflammatory T cells into the CNS. In patients with post-concussion syndrome after mild head injury, focal cortical dysfunction may occur in conjunction with the disruption of the blood–brain barrier [25].

Rasmussen's syndrome & CTLs

Lymphocytic infiltration, containing predominantly T cells and sparsely B cells, is found in surgically resected tissues from patients with Rasmussen's encephalitis [9]. Local CNS immune responses in Rasmussen's encephalitis include local clonal expansion of T cells responding to discrete antigen epitopes [26]. Destruction of neurons by granzyme B produced by CTLs has been demonstrated in resected tissues from