of both clinical entities were thought to rarely change from one clinical type to the other, it is important to understand that the conversion from DIHS to SJS/TEN is not the rare event: in many cases, SJS/TEN is usually preceded by DIHS. In these cases, occurrence of SJS-like lesions is delayed for a week after onset of clinical symptoms consistent with DIHS: this delay may be diagnostic of identifying the patients with DIHS evolving into SJS/TEN, because patients with widely distributed purpuric erythematous macules rapidly progressing into blisters and erosions over a period of a few days are likely to have SJS/TEN not associated with DIHS. Because these cases indicate that specific factors determining the expression of a particular disease phenotype may vary with time, detailed kinetic information on these patients would be helpful in determining disease expression.

Facial erythema and edema with pinhead-sized pustules as one of the relatively early symptoms of DIHS are often indistinguishable from those observed in AGEP. Clinicians who are less familiar with the clinical symptoms of DIHS and AGEP may experience the difficulties in assigning a specific diagnosis to patients presenting with facial erythema and edema associated with pustules. There is, however, considerable evidence that the two are distinct conditions with divergent clinical features. Nevertheless, the pattern of erythematous lesions in AGEP, initially with distribution around the flexural areas, is very different from DIHS where lesions usually occur on the face and upper trunk. The marked difference between the two can be also found in their disease course after withdrawal of the causative drug: spontaneous resolution of the pustules occurs in less than 15 days with characteristic desquamation [20], while DIHS usually runs a chronic unremitting course. Clearly, the clinical phenotype of severe drug eruptions varies with time and definitive diagnostic categorization is not always possible at the initial presentation.

Laboratory Findings

The peripheral blood usually shows marked leukocytosis with atypical lymphocytosis or eosinophilia of various degree. In some patients, leucopenia or lymphopenia may be seen, especially at the early stage of the illness [8, 12, 21]: this occasionally precedes leukocytosis. While eosinophilia can be seen in 60–70% of the patients in our series [8, 12], other recent studies reported that transient eosinophilia (95%) was far more frequently present [Kardaun et al., submitted] than previously reported. Occasionally, the number of monocytes is also increased, although this is a relatively late event as compared with neutrophilia and lymphocytosis, both of which can often be seen in the early stage of the disease. The increase in either CD4+ T cells or CD8+ T cells can be seen in the early phase of the disease. According to our series of 12 patients (6 male and 6 female, age range 25–70 years) with DIHS diagnosed and managed at our institution, CD4+ T-cell numbers initially increased at the early stage in >90% of these patients [22]; this increase, however, was followed by a gradual decrease reaching

normal values by 2 months after onset. In some patients, the increase in CD8+ T cell numbers was seen, although this difference was not reflected in clinical symptoms. A profound decrease in CD19+ B-cell numbers and CD56+ NK-cell numbers was observed at their initial presentation [23]. The subsequent decrease in CD4+ T cell numbers was usually coincident with improvements in clinical status. The degree of the increase in CD4+ T cell numbers best correlated with the severity of clinical symptoms, such as the extent of skin lesions and the magnitude of viral reactivations, as mentioned later.

A dramatic decrease in serum IgG, IgA, and IgM levels is typically observed at onset, and the lowest levels are usually detected a week after withdrawal of the causative drug [23]. Immediately 1–2 weeks after the nadir in their levels, the overshoot in their levels can be observed, and they eventually return to normal upon full recovery. Because these alterations in Ig levels during the course of the illness were never observed in patients with SJS/TEN and AGEP, this finding can only be diagnostic of DIHS when Ig levels are carefully measured at various points after onset. In some patients, this decrease may be only apparent when compared with those levels after full recovery, while those levels at onset may be within normal limits. Thus, it should be noted that Ig levels at a single time point are not sufficiently enough to conclude their decrease.

A marked increase in the serum alanine aminotransferase values can be seen in up to 70% of patients. In some patients, γ-glutamyl-transpeptidase, total bilirubin, and alkaline phosphatase increase to a variable degree. Such liver abnormalities often occur in association with the increase in circulating atypical lymphocytes, suggesting that activated lymphocytes may contribute to liver damage. Various forms of renal involvement have also been reported [24, 25], ranging from tubulointerstitial nephritis to granulomatous necrotizing angiitis. The mortality is likely to depend in part on the degree of renal involvement rather than hepatic involvement.

Although in earlier studies HHV-6 was thought to be the only virus that was reactivated in patients with DIHS [6], it has become clear that other herpesviruses, such as EBV, HHV-7, and CMV are also reactivated during the course of the disease [5, 26–28]. Our results of PCR analyses performed at various time points after onset showed that various herpesviruses sequentially reactivate during the course of DIHS in the order as demonstrated in graft-versus-host disease (GVHD) [27]: the cascade of reactivation events initiated by EBV or HHV-6 extends, with some delay, to HHV-7 as well, and eventually to CMV, as shown in figure 2. Our clinical observations demonstrated that reactivations of these herpesviruses can be detected coincident with the onset of various clinical symptoms, such as liver abnormalities in some patients while in other patients they occur without the evidence of overt clinical symptoms. In order to demonstrate full cascades of reactivation events during the course of DIHS, frequent sampling of blood at least on a weekly basis is needed, because the changes in viral loads are so rapid. Thus, the true peak of viral loads can easily be missed on a routine examination performed at a single time point on a routine basis.

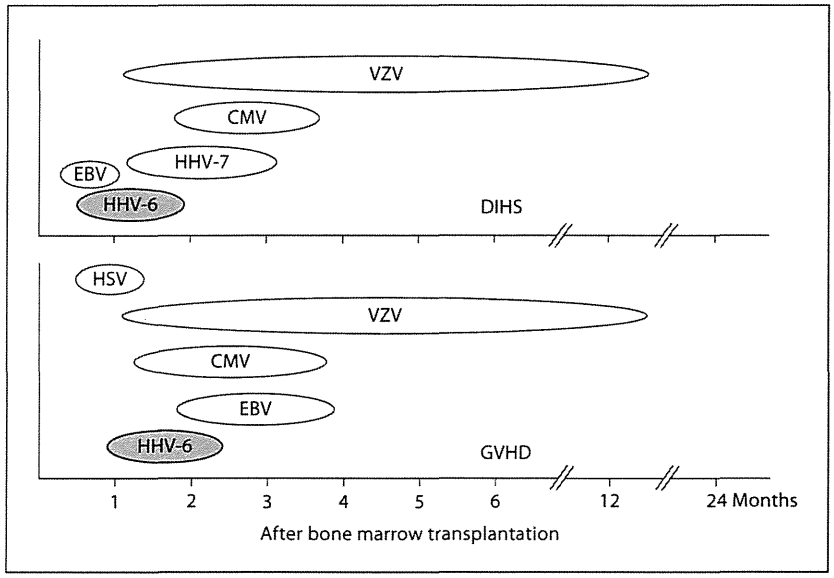

Fig. 2. The sequence of herpesvirus reactivation events observed in DIHS (upper) and GVHD (lower). Modified from our previous paper [12]. VZV = Varicella zoster virus.

Diagnosis of Drug-Induced Hypersensitivity Syndrome

The diagnosis of DIHS is usually not difficult for dermatologists who are familiar with clinical symptoms of DIHS, if a history of drug intake, particularly drugs listed in table 1, is sought in all patients presenting with fever, erythematous skin lesions predominating on the face and upper trunk, lymphoadenopathy, and other organ involvement. The diagnosis, however, can be challenging for physicians who have seen such patients before. There are a number of differential diagnostic considerations that may usually play a greater role in atypical or very early cases: they include EBV- or CMV-induced infectious mononucleosis (IM), measles, exfoliative erythroderma, a drug-induced erythrodermic condition, Kawasaki syndrome, Kikuchi-Fujimoto disease, and drug-induced pseudolymphomas. The clinical findings alone can be difficult to differentiate from IM: IM occurs most commonly in teenagers or young adults, and the eruption usually occurs 2–10 days after starting therapy with antibiotics which rarely cause DIHS, while DIHS typically occurs 3 weeks to 3 months after starting therapy with anticonvulsants in adults or elderly patients.

Although this syndrome had been recognized as a distinct disorder in the early 1960s, much of the confusion has resulted from the inconsistent and variable terminology and the lack of a specific and sensitive diagnostic test. In this regard, we and Hashimoto's group independently demonstrated that HHV-6 can be reactivated at a particular time point, 2–3 weeks after onset of rash in the vast majority of patients regardless of treatment [5, 6]. Since then, a strong association between HHV-6

Table 2. Drugs frequently causing DIHS/DRESS

• Carbamazepine	• Dapsone
• Phenytoin	• Salazosulfapyridine
• Phenobarbital	• Allopurinol
• Zonisamide	• Minocycline
• Mexiletine	• Abacavir[1]
• Lamotrigine	• Nevirapine[1]

[1] These drugs cause systemic hypersensitivity reactions with some peculiar symptoms [12].

reactivation and this syndrome has been supported by a large number of independent groups over the years in Japan. In 2006, we, a Japanese consensus group named the Japanese Research Committee on Severe Cutaneous Adverse Reaction established a set of criteria for diagnosis of this syndrome (table 2) and proposed the term 'DIHS' [7, 8]. DIHS is currently diagnosed by using the seven criteria in Japan: diagnosis of typical DIHS requires all seven criteria, although, in many cases, the criteria for DIHS are not all present on any given day. Our case series diagnosed by clinical and laboratory findings alone have shown that HHV-6 reactivation can be detected in the vast majority of patients who satisfy the other six criteria. The concept of 'atypical DIHS' can be used for patients with typical clinical presentations, in whom HHV-6 reactivation cannot be detected due to inappropriate timing of sampling or the lack of a specific test for detecting HHV-6 reactivation: the detection of HHV-6 reactivation can be evidenced by the significant rise in HHV-6 IgG titers or HHV-6 DNA levels.

Recently, an international consensus group named RegiSCAR has proposed a standardized scoring system for diagnosis [Kardaun et al., submitted], based on clinical and biological characteristics in 117 cases prospectively enrolled from 2005 to mid-2009. There is no fundamental difference in the clinical and laboratory findings except for HHV-6 reactivation between this system and our criteria, although the major concern is that, when this scoring system is used for diagnosis, the syndrome may be overdiagnosed or underdiagnosed due to the lack of a specific diagnostic test for HHV-6 reactivation. According to our experience, patients with clinical symptoms and laboratory findings consistent with those of DIHS but without the evidence of HHV-6 reactivation have shown to exhibit a tendency toward milder disease [7]. In our case series, patients who had more than two episodes of worsening after initial improvement, either treatment-related or -unrelated fluctuations, were more likely to run a chronic, unremitting course, probably due to repeated reactivations of various herpesviruses. The magnitude of HHV-6 reactivations as evidenced by the increase in HHV-6 DNA levels is thought to reflect the severity of inflammatory responses that occur in vivo in patients with DIHS. We recommend that HHV-6 testing be used to confirm a clinical diagnosis rather than simply as a screening tool.

The lymphocyte transformation test (LTT) [29] is a frequently used as a tool to confirm a clinical diagnosis of allergic drug reaction and determine the causative drug. We previously demonstrated that positive LTT reactions were obtained at the recovery stage but not the acute stage in DIHS, while in SJS/TEN and other types of drug eruptions, positive LTT reactions were only obtained when the test was performed at the acute stage [30]. Our analyses performed with the use of samples at various time points after onset showed that LTT reactions became positive from 5 weeks onward after onset in the majority of patients, regardless of whether patients were on therapy with prednisolone or not [30]. Because this finding was only observed in patients with DIHS, the LTT is a reliable method to define the causative drug in DIHS when the test is performed at the right timing. Ideally, this test should be done as soon as possible after presentation and should be repeated after 2 months. Negative LTT reactions at the acute stage could alternatively be interpreted as suggesting a diagnosis of DIHS.

Pathology

The histologic picture of DIHS is not diagnostic. The common pathological findings are superficial perivascular lymphocytic infiltrates and some extravasated erythrocytes and eosinophils. On rare occasions, DIHS may feature a lichenoid infiltrate with apoptotic keratinocytes, a finding frequently seen in other drug eruptions such as erythema multiforme type and SJS/TEN. Full-thickness epidermal necrosis and detachment can only be seen in patients with DIHS evolving into SJS/TEN. The pattern of inflammation in DIHS involves mixed infiltration composed of CD4+ and CD8+ T cells with hemorrhage. In our earlier study, high levels of HHV-6 genome and viral antigens were detected in infiltrating cells in the skin lesions taken at the early stage [5], despite the absence of HHV-6 DNA in the blood simultaneously obtained from the same patient. These results indicate that there exist other distinct, undefined compartments, such as skin, liver and lymph nodes, where herpesviruses can reactivate in sequential order independent of the blood. This may be reflected in differences in the nature of the localized immune process taking place in the target organs of DIHS.

Pathogenesis

Activated T cells seem to play an important role in DIHS, as suggested in other severe drug eruptions [19]. Previously, it was believed that DIHS merely represents an exaggerated, hyperinflammatory response with inflammation-induced viral reactivations and subsequent organ injury [9]. According to this theory, reactivations of herpesviruses specifically observed in patients with DIHS are a consequence, not a cause, of excessive activation of T cells. In this regard, we have suggested the existence of

a more complex scenario: sequential reactivations of herpesviruses would occur far earlier than onset probably due to protracted use of anticonvulsants, thereby causing the generation and activation of virus-specific memory CD8+ T cells. However, recent studies including our own have somewhat revised this theory and found that antiviral T cells can directly influence the course of DIHS and regulatory T cells confer protective immunity in this setting. In view of the fact that the clinical symptoms of DIHS remain dormant for prolonged periods after starting therapy with the causative drug, there could exist some mechanisms, whereby antiviral CD8+ T cell responses can be silenced to limit possible immunopathology before onset. If this balance mechanism is eventually disturbed, a condition is set that leads to onset of the disease. According to this scenario, memory T cells specific for a viral peptide presented in the context of certain HLA-A or -B could play a central role in the pathogenesis of DIHS, and drug antigens could serve to induce accidental activation of those virus-specific T cells with cross-reactivity to drug antigens. Consistent with this scenario, Hung et al. [31] provided evidence for a genetic predisposition in DIHS showing a strong association (100%) between allopurinol-induced DRESS and HLA-B*5801. Prospective studies of 40 patients presenting with well-characterized DRESS by Picard et al. [32] provide ample support for our scenario. They demonstrated that EBV, HHV-6, or HHV-7 reactivation can be detected in 76% of patients with DRESS and that the cutaneous and visceral symptoms of DRESS are associated with an oligoclonal expansion of activated memory CD8+ T cells that can specifically recognize one of viral antigens derived from herpesviruses. Importantly, viral replication has been shown to be enhanced by the causative drug, but not an irrelevant drug that has not been involved in the occurrence of DRESS [32]. A likely interpretation of these findings, in consideration of our own data, is that the cutaneous and visceral symptoms of DIHS can be mediated by the activation and migration into the target organ of antiviral CD8+ T cells resulting from sequential reactivation of herpesviruses.

If antiviral T cells play a central role in tissue injury, it is logical to ask by which mechanism(s) these antiviral T cells can be silenced over a prolonged period of time before onset. The most promising new insight into the protective mechanism(s) comes from the work from our group investigating the role of regulatory T (Treg) cells in patients with DIHS [19]. We have recently investigated whether Treg cell frequency and function can influence the clinical manifestations and course of DIHS. In this study, patients with TEN were also analyzed in comparison with DIHS. Dramatic expansions of fully functional CD4+CD25+FoxP3+ Treg cells were specifically found in the acute stage of DIHS [19]; in contrast, in TEN their capacity to migrate into the skin and to suppress the activation of Teff cells was profoundly impaired during the acute stage, although they are present in normal frequency in the blood. These expanded Treg cells have been shown to inhibit drug-induced cytokine production by Teff cells in vitro, indicating that the expanded Treg cells could serve to inhibit activation of antiviral T cells for a prolonged period of time before onset of DIHS, and induce sequential reactivations of herpesviruses. Our further unpublished

observations show that the causative drug can trigger the expansion of Treg cells from patients with DIHS. Our findings provide explanations for why the onset of DIHS is delayed in relation to the introduction of the causative drug, and why severe epidermal damage cannot be detected in the skin lesions of DIHS despite activation of Teff cells, why viral reactivations are induced, and why positive LTT reactions cannot be detected during the acute stage. In view of their ability to induce B cell death [33], a decrease in serum Ig levels and B cell number specifically observed during the acute stage would be explained by expansions of functional Treg cells.

Surprisingly, the Treg cells gradually lose their original suppressing function when contracted upon resolution of IDHS [19]. In contrast, a functional impairment of Treg cells during the acute stage of TEN was restored upon resolution. This progressive dysfunction of Treg cells specifically observed after resolution of DIHS could be due to their exhaustion as a consequence of repeated activation of Treg cells in response to excessive activation of Teff cells including antiviral T cells driven by a high viral load in patients.

Complications and Long-Term Sequelae

Our series of patients and a review of the English literature have suggested the following features of the natural history of DIHS. Less than 10% of patients die within 1 year after onset, and autoimmune disease or production of autoantibodies occur as a sequela of DIHS in 10% of surviving patients, regardless of whether they were treated with systemic corticosteroids. Because they appear for several months to years after the acute illness was resolved, it is difficult to find a link between preceding DIHS and the subsequent autoimmune diseases unless special attention is given to a history of a clinical illness compatible with DIHS. It should be recognized that they cannot necessarily occur immediately after resolution of DIHS but rather occur after a disease-free interval of several months to years and that there is the long prodromal period preceding clinical onset of autoimmune diseases [34]. These autoimmune diseases include type 1 diabetes mellitus [35–38], autoimmune thyroid disease [8, 12, 38], sclerodermoid GVHD-like lesions [39] and lupus erythematosus [34, 40]. In a patient who subsequently developed GVHD-like lesions, antinuclear antibody (ANA) was negative during the course of DIHS and became detectable (1:40), coincident with the development of alopecia: a dramatic increase in ANA (1:5,120) was eventually found 4 years after onset of DIHS, at her initial presentation to our Department because of sclerodermoid GVHD-like lesions, indicating that the disease process of DIHS may act as a trigger for the subsequent development of autoimmune disease [39]. Given the strong association between EBV infection and systemic lupus erythematosus (SLE) [41, 42], it is likely that EBV reactivations occurring during the episode of DIHS could profoundly influence the autoimmune sequelae of DIHS. Indeed, EBV reactivations were confirmed on two occasions, during the episode of DIHS and at

the time of the presentation with clinical manifestations of SLE in our reported case [34, 40]. In addition to the role of EBV reactivations, a gradual loss of Treg function after resolution of DIHS [19] could increase the risk of subsequently developing autoimmune disease.

Management of Drug-Induced Hypersensitivity Syndrome

Early recognition of clinical symptoms compatible with DIHS is essential in improving patient outcomes. Because paradoxical deterioration of clinical symptoms and laboratory findings is often seen 3–4 days after withdrawal of the causative drug, a concern of an underlying infection may be generated; and, as a result, empirical treatment with antibiotics or nonsteroidal anti-inflammatory drugs may be initiated, which often confuse or worsen the clinical picture probably due to unexplained cross-reactivity to these drugs. The use of those drugs should be avoided, particularly during the acute phase.

Systemic corticosteroids is the mainstay of treatment, particularly in the earlier stages of the disease. Rapid resolution of rashes and fever occurs within several days after starting a moderate dose of systemic corticosteroids (prednisolone, 40–50 mg/day). Because marked deterioration of various clinical symptoms is frequently seen with abrupt discontinuation or rapid tapering of corticosteroids, corticosteroid dose should be reduced gradually even upon resolution of clinical manifestation: tapering corticosteroids more gradually over a prolonged period of time (usually 6–8 weeks) can help to limit the severe flare-ups. One should recognize that patients with DIHS are at greater risk of subsequently developing the wide spectrum of immune reconstitution syndrome (IRS) ranging from CMV disease to autoimmune disease [8, 12, 22, 34] (table 3), and the use of systemic corticosteroids represents an important factor that increases the risk of disease progression to full manifestations of IRS upon the withdrawal or reductions. Indeed, HHV-6 and CMV, but not EBV, viral loads were significantly higher in patients with DIHS receiving systemic corticosteroids compared with those without corticosteroid therapy [Ishida et al., submitted]. This finding indicates that the degree and duration of HHV-6 and CMV reactivations would be greatly influenced by the use of immunosuppressive drugs. Nevertheless, this effect of corticosteroids on viral reactivations is likely to be an unanticipated consequence of a tapering corticosteroid dose, because our frequent monitoring of viral loads in patient with DIHS revealed that the increase in CMV viral loads coincided with a tapering of corticosteroid dose [43]. Given the high risk of sequelae from CMV reactivation in patients with DIHS [43], the direct anti-CMV medications with a gradual reducing dose of corticosteroids may help to avoid disease progression to full manifestations of IRS [22].

The use of intravenous immunoglobulin (IVIG) has so far only been assessed in some patients; however, our trials of combining treatments, giving IVIG (0.1 g/kg per

Table 3. Reported clinical illness consistent with IRS in HIV-negative hosts [22]

Mycobacterium avium complex infection
Tuberculosis
Cryptococcosis[1]
Herpes simplex[1]
Herpes zoster[1]
Hepatitis C virus
Hepatitis B virus
CMV[1]
Kaposi sarcoma
Sarcoidosis
Graves' disease
Hashimoto thyroiditis[1]
DIHS

[1] Infectious and autoimmune diseases often observed during the course of DIHS or long after its resolution.

day for 3 days) together with systemic corticosteroids, have failed to show extra benefit compared with corticosteroids alone. Because patients with moderate disease can often recover from this syndrome by supportive care without the need of systemic corticosteroids within 3 weeks, the use of systemic corticosteroids is not necessarily recommended as a treatment option of DIHS. Particularly, a small dose (prednisolone, 10–20 mg/day) of systemic corticosteroids followed by small increments in dosage at short intervals should be avoided even for mild cases, because this may not be sufficient to ameliorate clinical symptoms and may result in unnecessarily protracted use of corticosteroids. Thus, although systemic corticosteroids have become accepted as the gold standard treatment for DIHS, it remains to be determined whether treatment with systemic corticosteroids is also beneficial from a viewpoint of disease outcome and sequleae. Nevertheless, the benefit is greatest during the first 2–3 weeks when treatment was given early. Likewise, there was also no significant improvement in patients treated with corticosteroids for other important outcomes including time to discharge, death and disability after 1 year. Our longitudinal PCR analyses of viral loads in patients with DIHS justify the frequent monitoring of viral reactivations to predict and improve the short-term or long-term outcome.

Conclusion

The development of an internationally standardized scoring system to clearly identify patients with DIHS will be critical in treating those who had suffered from preventable

morbidity and mortality. Considerations for the development of therapies that can reduce the risk of long-term sequelae such as autoimmune disease would seem a reasonable path to pursue.

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重症薬疹の治療指針*

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要約 Stevens-Johnson症候群，中毒性表皮壊死症の治療では，副腎皮質ステロイド薬全身投与を第一選択とし，重症例では発症早期にステロイドパルス療法を含む高用量のステロイド薬の投与を行う．ステロイド薬で効果がみられない場合には免疫グロブリン製剤静注療法や血漿交換療法を併用する．また，治療経過中に発症する感染症には十分に注意する．薬剤性過敏症症候群でもステロイド薬の全身投与が基本となるが，紅皮症状態，心不全，腎不全などの重篤な基礎疾患を有している場合には，早期からの投与が推奨される．経過中にさまざまなヒトヘルペスウイルス再活性化や感染症を引き起こすので，ステロイド薬の減量は急がずに行い，再燃時のステロイド投与は慎重に行う．発症5～7週目に生じるサイトメガロウイルス感染症は致死的な状態をもたらす場合が多いので，その徴候があれば，抗ウイルス薬を投与して対応することが大切である．

キーワード Stevens-Johnson症候群，中毒性表皮壊死症，薬剤性過敏症症候群，ステロイド全身療法，ヒト免疫グロブリン静注療法

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はじめに

重症薬疹にはStevens-Johnson症候群(Stevens-Johnson syndrome：SJS)，中毒性表皮壊死症(toxic epidermal necrolysis：TEN)，薬剤性過敏症症候群(drug-induced hypersensitivity syndrome：DIHS)などが含まれる．この中でSJSとTENにおいては2009年に治療指針[1]が発表され，治療の目安として広く普及してきた感がある．しかし，DIHSの治療についてはステロイドの使用の是非，その減量のスピードなどについてまだ統一された見解はなく，混沌としている．ここでは重症薬疹の治療指針について述べる．

治療の概要

現在，SJSとTENは一連の疾患ととらえられており，治療の基本的な考え方は同じである．SJS/TENを疑った場合には，まず被疑薬の中止を行う．通常，副腎皮質ステロイド薬を第一選択とし，重症例では発症早期にステロイドパルス療法を含む高用量のステロイド薬[1,2]を投与する．ステロイド薬の全身投与は発症早期に開始することが望ましい．発症後，表皮剥離が全身に及んだ段階でのステロイド薬開始は敗血症などの感染症を助長する可能性が高い．皮疹が軽度でも眼表面

* Guidelines of treatment for severe drug eruptions

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〔略語〕SJS：Stevens-Johnson syndrome, TEN：toxic epidermal necrolysis, DIHS：drug-induced hypersensitivity syndrome, CMV：cytomegalovirus, IVIG：intravenous immunoglobulin

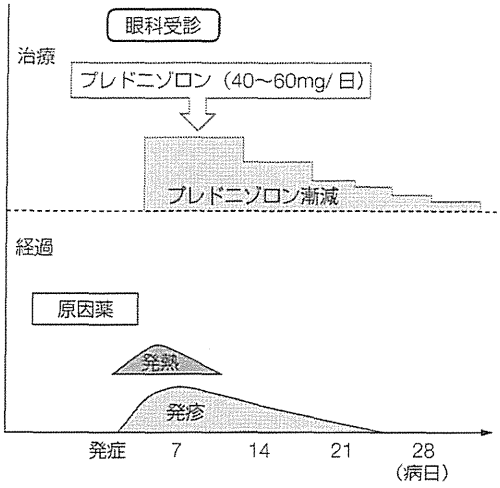

図1　Stevens-Johnson 症候群の治療例

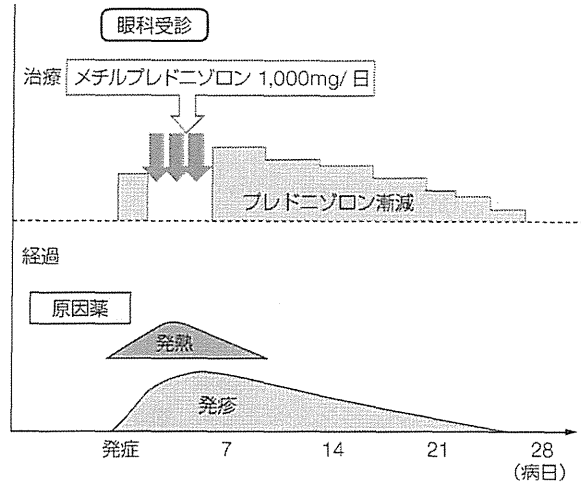

図2　中毒性表皮壊死症の治療例

上皮のびらん，あるいは偽膜形成などの高度な粘膜疹がみられる場合には，眼科医の診察を受けさせ，初期からパルス療法などステロイド薬の大量投与を選択する．

SJS から TEN の進展やステロイド薬の効果が不十分と判断した場合には直ちに，免疫グロブリン製剤静注療法[3]や血漿交換療法を併用する．特に TEN では発症から 1 週間の治療の選択が予後に大きな影響をもたらすことに留意する．

皮疹部の局所処置，眼科的管理，補液・栄養管理，感染防止なども SJS/TEN 治療の重要なファクターととらえて治療を進める．

DIHS では初診時に一見軽症にみえても原則として入院させて治療する．ステロイド薬の全身投与が基本的治療となる．初期量は 1～2 週間はがっちりと投与し，漸減は緩徐に行う．発疹，発熱，肝腎障害などの再燃時には検査データを詳細に検討し，ステロイド量の維持あるいは増量を判断する．経過中に辺縁系脳炎，肺炎などのさまざまな臓器障害に加えて，発症から 5～7 週目頃に致死的障害をもたらすサイトメガロウイルス（cytomegalovirus：CMV）感染症が生じる可能性を予測して治療を進める．CMV の再活性化時には抗ウイルス薬を投与する．

目的・目標

SJS/TEN の治療の目的は表皮の壊死病変の進行を最小限に抑え，上皮化までの二次感染を防ぎ，後遺症・続発症の出現を回避することにある．重篤な感染症を合併している場合や感染症の併発が認められる場合にはステロイド薬に加えて抗菌薬などを投与し，感染対策を十分に行う．また，視力障害，瞼球癒着，ドライアイなどの眼合併症の発症を最小限にするために，初期から眼科専門医の診察・加療を受けさせる．粘膜症状の長期間の持続により，慢性閉塞性呼吸器疾患や外陰部癒着などの瘢痕性病変が起きないように治療を進める．

DIHS では経過中に再燃や多彩な臓器障害，ヒトヘルペスウイルス再活性化による感染症などを引き起こす．短期的な目標としては，再燃を繰り返さないようにすること，CMV 感染症[4]などを発症させないようにすることである．さらに，長期的視点では DIHS 回復後数年経過してから発症する自己免疫疾患の発症を回避することが挙げられる．

治療の実際

1. SJS/TEN

SJS/TEN ではステロイド薬の全身投与は通常，プレドニゾロンまたはベタメタゾン，デキサメタゾンをプレドニゾロン換算で，中等症は 0.5～1 mg/kg/日，重症は 1～2 mg/kg/日で開始する．治療効果の判定には，紅斑・表皮剥離・粘

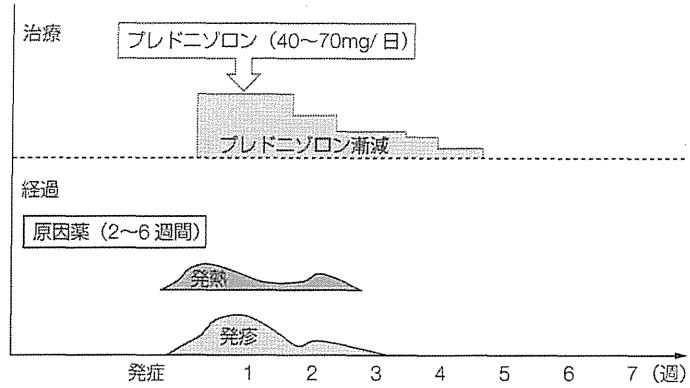

図3　薬剤性過敏症症候群の治療例

膜疹の進展の停止，びらん面からの滲出液の減少，解熱傾向，末梢血白血球異常の改善，肝機能障害などの臓器障害の改善などを指標とする．

重症例や急激に進展する症例ではステロイドパルス療法を行うのが適している．パルス療法は，メチルプレドニゾロン500～1,000 mg/日を3日間投与する．中等症の場合は，より少量(250 mg/日)の投与で効果がみられることがある．初回のパルス療法で効果が十分にみられない場合，または症状の進展が治まったのちに再燃した場合は，数日後にもう1サイクル施行するか他の療法を併用する．パルス療法直後のステロイド投与量の選択は重要で十分量(プレドニゾロン換算で1～2 mg/kg/日)を投与し，前述したような指標を参考にしながら漸減する．減量は個々の症例の回復の程度により調整する(**図1，2**)．さらに，発熱，紅斑・表皮剝離，粘膜病変などを目安として，効果がみられないと評価した場合には，ステロイド薬の増量，ヒト免疫グロブリン製剤静注(intravenous immunoglobulin：IVIG)療法や血漿交換療法などを併用する[1]．IVIGは5～20 g/日，3～5日間を1サイクルとして投与する．また，ステロイド療法で症状の進行がくい止められない重症例に血漿交換療法を併用療法として用いる．この血漿交換療法は重症感染症などでステロイド薬の使用が困難な場合にも施行することができる．

2. DIHS

DIHSでは被疑薬を中止すると同時に発症時に服用していた薬剤も可能な限り中止することが望ましい．しばしば原因薬中止数日後に発熱の上昇，顔面の浮腫や発疹の増悪がみられることに留意する[5]．高齢，紅皮症状態の場合，心不全・腎不全(透析中)などの重篤な基礎疾患を有している場合には，早期からのステロイド投与が推奨される．ステロイド薬の初期量はプレドニゾロンまたはベタメタゾン，デキサメタゾンをプレドニゾロン換算で，30～70 mg/日(または0.5～1 mg/kg/日)で開始する．初期量は発疹のみならず，臓器障害の程度，先行する治療経過などを考慮して決定する．初期量は原則として7～14日間投与する．この初期量のステロイド投与期間が短いと再燃をまねくことが多い．また，ステロイドの急激な減量はDIHSにおいて潜伏感染の顕性化をまねくことがあるので，慎重に進める必要がある．ステロイド薬の減量は，臨床症状の軽快に伴い1～2週間ごとに5～10 mg/日ずつ行う(**図3**)．また，経過中に，ヒトヘルペスウイルス再活性化による発疹，発熱，肝・腎障害などの再燃が認められることがある．このときには，血液・生化学，免疫血清(IgGなど)，可能ならばウイルス量などの検査値を評価しながら，ステロイド薬は症状が軽減するまで数日間同量を維持する．多くの場合このステロイド量の維持で症状は改善する．しかし，発熱が持続し重篤な臓器障害の発現やSJS/TENに類似する表皮の壊死性病変・粘膜病変などが出現した場合には，ステロイド薬の増量やステロイドパルス療法などを検討する．パルス療法

は，メチルプレドニゾロン500～1,000 mg/日を3日間投与する．パルス療法直後のステロイド投与量は原則としてプレドニゾロン換算で1 mg/kg/日を投与し，以後漸減する．

その他の治療法としてはIVIG療法がある[6]．重症例には，5～20 g/日，3～5日間を1サイクルとして投与することもある．ただし，漫然と長期投与することは避けねばならない．また，血漿交換療法はSJS/TENとのオーバーラップが考えられる場合に選択肢となる．

DIHSの経過中，特に発症5～7週目にCMVの再活性化(末梢血のCMV抗原血症の検出)により，肺炎・消化管出血・腸炎・心筋炎などのCMV感染症が発現した場合には，抗ウイルス薬〔ガンシクロビル(900～1,800 mg/日)など〕を投与する．原則として抗ウイルス薬はCMVの抗原血症の陰性化まで継続することが推奨される．なお，教室経験DIHS例で補液のみによる保存療法群とステロイド治療群を比較してみると，CMV再活性化はステロイド治療群で有意に検出されていた．

考　按

SJS/TENでは表皮剝離の進行が非常に速いため，1つの治療で効果が得られない場合には直ちに次の治療へ変更・追加治療などの判断をして治療を進めていくことが要求される．海外ではSJS/TENの治療としてシクロスポリン投与も試みられ，SCORTEN[7]を用いた評価ではシクロスポリンはSJS/TEN治療の1つのオプションとなると報告している[8]．また，乾癬の治療薬として投与されているTNF(tumor necrosis factor)-α阻害薬をSJS/TENに使用して効果が得られたという報告もある[9]．いずれの治療においても経過中にみられる肺炎，敗血症などの感染症が致命的になることが多い．

一方，DIHSではSJS/TENと異なり，発症から数日間は経過観察あるいは全身状態を見極める時間的余裕がある．ステロイド治療を開始した場合はその急激な減量により起こる免疫再構築症候群としてのニューモシスチス肺炎やCMV感染症などに十分に注意する．また，この感染症に対して投薬を行う際にはDIHSでは薬剤の多剤感作が生じやすいことや，抗ウイルス薬ではそれ自体で血球系の減少や肝障害が引き起こされることを認識して使用することが大切である．

近年，DIHS回復後に自己免疫性甲状腺炎，劇症1型糖尿病，エリテマトーデス，強皮症様病変などの自己免疫疾患が発症する症例[10]が散見されている．DIHSの治療では，ステロイド薬投与中に発症しやすい感染症の短期的なリスクと回復後の自己免疫疾患発症の可能性という長期的なリスクがあることを考慮して治療を進めていく必要がある．

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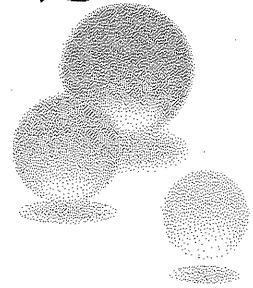
重篤副作用発現の遺伝子マーカー



鹿庭なほ子
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特異体質が原因で発症するといわれているタイプBの副作用は，発生頻度は低いものの，重篤で最悪の場合には死に至るために，薬物治療を開始する前に高リスク患者を識別することが望まれていた。スティーブンス・ジョンソン症候群，中毒性表皮壊死症などの重症薬疹およびアレルギー性薬剤性肝障害はタイプB副作用の代表であるが，近年，これらの副作用の発症には，ヒト白血球抗原HLAの特定のタイプが関与しているというデータが蓄積されるようになってきた。現在すでに一部の地域では，重症薬疹の発症を未然に防ぐため，薬物治療を開始する前に*HLA-B*1502*（カルバマゼピン），*HLA-B*5701*（アバカビル），*HLA-B*5801*（アロプリノール）の検査が義務づけられている。

Key word スティーブンス・ジョンソン症候群，中毒性表皮壊死症，重症薬疹，薬剤性肝障害，HLA

タイプB副作用

薬物による副作用の多くは，薬理作用の延長上で発生するか（タイプA副作用），あるいは，薬物の標的器官とは別の器官に対して，薬物の活性に基づいてはいるが望ましくない反応が生じるために起こる（タイプC副作用）。このような副作用は，医薬品の開発中からその発生を予測することが可能であり，また，薬物動態依存的に発症するので投与量を調整することにより軽減させることも可能である。しかしまれには，タイプBに分類される副作用のように，薬物の薬理作用や活性とは無関係の反応が標的器官とは無関係の臓器で発生することがある。このような副作用は特異体質によって発生することが多く重篤化しやすい。また，発生頻度が非常に低いために医薬品の開発中にその発生を予測することが困難で，市販後に多くの患者に使われてはじめて経験される点においても，医療従事者ならびに製薬企業泣かせの副作用である。

近年，このような重篤副作用の危険因子として遺伝子マーカーが報告されるようになり，そのうちのいくつかは重篤副作用の発生を防止するために臨床の場で利用されるようになった。本稿では，タイプB副作用の代表である重症薬疹およびアレルギー性の薬剤性肝障害の発症と関連する遺伝子マーカーについて紹介する。

重症薬疹関連の遺伝子マーカー

1．重症薬疹の種類

薬疹はしばしばみられる副作用であるが，最も重篤な薬疹として，スティーブンス・ジョンソン症候群（SJS），中毒性表皮壊死症（TEN）および薬剤性過敏症症候群（DIHSまたはHSS）があげられ，致死率はそれぞれ5％，30％，10％に達する。SJS/TENは，皮膚や粘膜の発疹，水疱化，剥離を主症状とし，しばしば高熱と臓器障害を伴い，回復後も目や気道に後遺症が残ることがある。SJSとTENは，重篤度の異なる同一の副作用で，皮膚の

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表1　重症薬疹の遺伝子マーカー

原因薬物	副作用	遺伝子マーカー	民族	ケース群 キャリアー頻度（感度）	ケース群 アレル頻度	対照群 キャリアー頻度（特異度）	対照群 アレル頻度	p値	オッズ比	引用文献
カルバマゼピン	SJS/TEN	*HLA-B*1502*	漢民族（台湾）	59/60		6/144		2.61E−41	1,357	1)
			タイ人	37/42		5/42		2.89E−12	54.76	3)
		*HLA-B*1511*	日本人	4/14	4/28 (14.3%)		1%	0.0004	16.3	5)
			韓国人	3/7	3/14 (21.4%)		3.9%	0.002	18.4	6)
		*HLA-A*3101*	日本人	5/6		54/420		2.35E−4	33.9	8)
			白人	5/12		10/257		8.0E−5	25.93	9)
	MPE/HSS	*HLA-A*3101*	漢民族（台湾）	8/31		4/144		0.0021	12.17	1)
アロプリノール	SJS/TEN/HSS	*HLA-B*5801*	漢民族（台湾）	51/51		20/135		4.7E−24	580.3	10)
			韓国人	24/26		6/57		2.45E−11	97.8	11)
	SJS/TEN		日本人		10/36 (27.8%)		0.6%	5.39E−12	62.8	12)
			白人	15/27		28/1,822		<1.0E−8	80	2)
アバカビル	HSS	*HLA-B*5701*	白人※	42/42		8/202			1,945	13)
			黒人※	5/5		2/206			900	13)
メタゾラミド	SJS/TEN	*HLA-B*5901*	日本人	3/3						14)
			韓国人	5/5		20/485		<0.001	249.8	15)

※：アバカビルに対するパッチテスト陽性者のみを対象にした結果

剥離面積が体表面積の10%未満の場合をSJS，それ以上の場合をTENという。同じく皮膚障害を伴うが，粘膜の関与が少なく，高熱，肝機能障害，リンパ節の腫脹，ヘルペス・ウイルスの関与を伴うのがDIHSである。わが国におけるSJS/TENの原因薬物としては，アロプリノール，カルバマゼピン，総合感冒薬，ロキソプロフェンなどが恒常的に多く，抗生物質，合成抗菌薬，消炎解熱鎮痛薬，抗てんかん薬なども上位を占めている。

2. 原因薬物別の遺伝子マーカー

HLA（ヒト白血球抗原）の特定のタイプが重症薬疹発症の危険因子であることを示唆するデータが蓄積されつつあり，表1に原因薬物別に重症薬疹の発症と関連する遺伝子マーカーをまとめた。

これまでに，カルバマゼピン誘引性SJS/TENと*HLA-B*1502*との強い相関性が，台湾の漢民族[1]，欧州在住のアジア人[2]，タイ人[3]，インド人[4]など主として東南アジア系の患者で確認されてきた。一方，このような関連は白人[2]，日本人[5]，韓国人[6]では確認されておらず，また漢民族にあってもSJS/TEN以外の重症薬疹と*HLA-B*1502*との関連性は認められていない。ところが，日本人と韓国人においては，カルバマゼピン誘因性SJS/TENと*HLA-B*1511*との関連が認められた。*HLA-B*1511*は，*HLA-B*1502*と同一の血清型HLA-B75に属し，これまでにもタイ人[3]，漢民族，インド人[4]のカルバマゼピン誘因性SJS/TEN患者で，やはりHLA-B75に属する*HLA-B*1508*，*HLA-B*1511*，*HLA-B*1521*の保有者が報告されてきた。*In vitro*発現系を用いた研究では，*HLA-B*1502*発現細胞と同様に，これらのHLA-B75のサブタイプを発現した細胞はカルバマゼピンを抗原提示し，細胞障害性T細胞の攻撃を受けることが示されている[7]。HLA-B75の母集団頻度はアジアの多くの国々では1%以上であり，これらのことは，*HLA-B*1502*を含めたHLA-B75がアジア人全体におけるカルバマゼピン誘因性SJS/TEN発症の危険因子であることを示している。一方，白人や黒人ではHLA-B75の母集団頻度が極

めて低く，HLA-B75をカルバマゼピン誘因性SJS/TENの危険因子として考慮する必要性は低い。HLA-B75のほかに，白人と日本人においては*HLA-A*3101*がカルバマゼピン誘因性SJS/TENの遺伝子マーカーとして報告されている。*HLA-A*3101*は，漢民族を対象にした研究では，SJS/TENを除くカルバマゼピン誘因性重症薬疹の遺伝子マーカーとして報告されたものであるが[1]，興味深いことに，日本人および白人では*HLA-A*3101*はSJS/TENの発症にも関与していることが示唆された[8),9)]。

アロプリノール誘因性SJS/TENの遺伝子マーカーとしては，白人[2)]，アジア人[10)-12)]を問わず，*HLA-B*5801*が報告されている。表1に示すようにアロプリノール誘因性HSSの患者にも*HLA-B*5801*の保有者がいることから，*HLA-B*1502*と異なり*HLA-B*5801*は民族や副作用のフェノタイプを問わず，アロプリノール誘因性重症薬疹の遺伝子マーカーであるといえよう。*HLA-B*5801*の母集団頻度が5％以上と比較的高い漢民族や韓国人では感度あるいはオッズ比が高く，母集団頻度が1％以下と低い日本人や白人では感度が低い。

HIV治療薬であるアバカビルは，白人では服用を開始してから6週間以内に5～8％の患者でHSSを発症するといわれているが，白人および黒人では*HLA-B*5701*がアバカビル誘因性HSSの発症と強い関連があると報告された[13)]。*HLA-B*5701*の母集団頻度が低い台湾や韓国のHIV患者では，これまでのところ，*HLA-B*5701*の保有者は1例しか報告されておらず，また，台湾人，韓国人，日本人においてはアバカビル誘因性HSSの発症率も低い。

これに対して，メタゾラミド誘因性のSJS/TENは日本人や韓国人で発症率が高い。メタゾラミド誘因性SJS/TENの危険因子としてはHLA-B59/*HLA-B*5901*が報告されているが[14),15)]，HLA-B59の日本人および韓国人における母集団頻度は1～2％であり，白人では保有者はほとんどいない。

以上より，重症薬疹の遺伝子マーカーは，原因となる薬物ごとに異なっていることが理解できるであろう。また，これらの遺伝子マーカーには一見民族差があるようにみえる。その要因としては，遺伝子マーカーの母集団におけるアレル頻度が上げられ，遺伝子マーカーの母集団頻度が高い地域では，感度（患者におけるマーカー保有率）が高く，また，当該薬物誘因性の重症薬疹の発生頻度も高いという現象がある。

3．臨床における遺伝子の事前検査の利用

後ろ向き試験による探索研究で，いくつかの薬物が原因で発症する重症薬疹の遺伝子マーカーが見つかってきたが，そのうち，*HLA-B*1502*および*HLA-B*5701*については，事前の遺伝子検査が重症薬疹の予防に有効であるかどうかについて，何千人もの被験者が参加した大規模な検証試験が行われ，いずれの遺伝子検査も重症薬疹の発症を未然に防ぐことに効果があることが示された[16),17)]。後ろ向き試験によるデータの蓄積，および前向きの検証試験の結果を受けて，現在，欧米ではアバカビルによるHSS発症の予防のために*HLA-B*5701*の事前検査が義務づけられている。米国においては，カルバマゼピン誘因性SJS/TENの予防のために，危険性の高い民族に対して*HLA-B*1502*の検査を行うことが義務づけられている。台湾では，*HLA-B*1502*の検査に加えて，アロプリノール誘因性重症薬疹の防止のために*HLA-B*5801*の検査が義務づけられている。このように，臨床の場において，すでに遺伝子マーカーは重症薬疹防止のための個別化医療に利用されているのである。

アレルギー性薬剤性肝障害関連の遺伝子マーカー

薬剤性肝障害は，医薬品が市場から撤退する最大の理由であり，わが国の医薬品医療機器被害救済制度で救済される副作用では重症薬疹に次いで多い。薬剤性肝障害の発生メカニズムとしては，薬物が肝毒性を有する中毒型，代謝酵素活性の異常で肝毒性のある薬物あるいは代謝物が蓄積する代謝酵素特異体質型，およびアレルギー性特異体質型に分けられ，障害の部位からは，肝細胞障害型，胆汁うっ滞型，両者の混合型に分けられる。わが国で原因薬物として多く報告されるものは，テルビナフィン塩酸塩，カルバマゼピン，チクロピジン塩酸塩，高脂血症治療薬，ロキソプロフェンナトリウムなどであ

るが，海外では，flucloxacillin（日本では販売されていない），アモキシシリン/クラブラン酸カリウム配合剤が断然多い。

代謝酵素特異体質性肝障害では，PhaseⅡの代謝酵素であるNAT2をコードする遺伝子の変異が関与するサルファ剤やイソニアジドによる薬剤性肝障害，*GSTT1*と*GSTM1*の欠損型多型が関与するtroglitazoneやtacrineによる薬剤性肝障害が有名であるが，アレルギー性薬剤性肝障害では，近年，重症薬疹と同様に，発症の危険因子として*HLA*が報告されるようになった。Flucloxacillin誘因性薬剤性肝障害では，アバカビル誘因性HSSの遺伝子マーカーでもある*HLA-B*5701*との関連が報告されている（オッズ比80）[18]。また，日本人で発症率が高いチクロピジン誘因性薬剤性肝障害では，*HLA-A*3303*との関連が報告されている（オッズ比13）[19]。アモキシシリン/クラブラン酸誘因性，lumiracoxib誘因性およびラパチニブ誘因性薬剤性肝障害では，それぞれ*HLA-DRB1*1501*（オッズ比9.25），*HLA-DQA1*0102*（オッズ比6.3），*HLA-DQA1*0201*（オッズ比9.0）の関与が報告されている[20)-22)]。重症薬疹と同じく，薬剤性肝障害においても発症に関与する遺伝子マーカーは原因薬物特異的である。

薬剤性肝障害の発症と関連する遺伝子マーカーについては，重症薬疹の遺伝子マーカーとは異なり，いまのところは臨床現場における利用，すなわち薬物治療を開始する前の遺伝子事前検査を推奨するまでには至っていない。

おわりに

重篤副作用の危険因子探索研究の成果はめざましく，一部は臨床の場で利用され始めた。しかし，重篤副作用の遺伝子マーカーが明らかにされたのは，一部の薬物が引き起こすほんの一握りの副作用にすぎない。したがって，依然として医療関係者が副作用の兆候を早期に把握し重篤化させないようにすることは重要である。厚生労働省は，早期に副作用を発見することを目的に，2005年度から患者および臨床現場の医師・薬剤師に向けて「重篤副作用疾患別対応マニュアル」を提供してきた。これらのマニュアルは，医薬品医療機器総合機構のHP（http://www.info.pmda.go.jp/juutoku/juutoku_index.html）からダウンロードできる。薬剤師の方々も，ぜひこのマニュアルを活用して重篤副作用の予防に努めていただきたいと思う。また国立医薬品食品衛生研究所では，SJS/TEN，横紋筋融解症，間質性肺疾患の症例を集積して副作用の遺伝子マーカーの探索研究を進めている。副作用発生の情報を得たならば，SJS/TENの場合はjscar@nihs.go.jp，横紋筋融解症の場合にはjmyo@nihs.go.jpに，また，間質性肺炎の場合にはjlung@nihs.go.jpにご連絡をお願いしたい。

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