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## NATスクリーニングのプールサイズ縮小による効果と解析

大阪府赤十字血液センター

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【はじめに】輸血用血液製剤の安全性の向上を目的として，2004年8月よりNATスクリーニングのプールサイズを50から20に縮小した。今回，大阪センターで検出されたHBV-NAT陽性事例を基にプールサイズ縮小の効果等について解析を行ったので報告する。

【対象】大阪センターにおいて50プール及び20プールで検出されたHBV-NAT陽性事例の合計81人を対象とした。

【結果】HBV-NAT陽性数

| | | 50プール | 20プール |
|---|---|---|---|
| 陽性者 | | 55人（2.72） | 26人（2.50） |
| HBc抗体（EIA法） | 陽性者 | 3人：5.5%（0.14） | 9人：34.6%（0.86） |
| | 陰性者 | 52人：94.5%（2.57） | 17人：65.4%（1.63） |
| 100コピー未満/mLの陽性者 | | 1人：1.8%（0.04） | 6人：23.1%（0.57） |
| 1,000コピー未満/mLの陽性者 | | 14人：25.5%（0.69） | 8人：30.8%（0.77） |
| 50～60歳代の陽性者 | | 4人：7.3%（0.19） | 10人：38.5%（0.96） |

（　）内は10万人あたりの本数

HBc抗体陽性の12人中，11人は50～60歳代でウイルス量が1,000未満コピー/mLであり，残りの1人は28歳でウイルス量が$1.7\times10^5$コピー/mLであった。また，12人中10人の献血者について医師による面談及びフォローアップを行ったところ，急性肝炎の発症等に関する申告はなく，来所時の検査結果によるウイルスコピー数及びウイルスマーカーの変動はなかった。

【考察】①プールサイズ縮小後に100コピー未満/mLのHBV-NAT陽性者の比率が高くなっていることから，縮小による効果があると思われた。②追跡調査，遡及調査及び医師の面談等による総合的な解析によりHBV低濃度キャリアが疑われる献血者がプールサイズ縮小後に多く検出していることが推察された。

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**研究報告の概要**

輸血伝播性 C 型肝炎ウイルス（TT-HCV）が疑われた症例はブリティッシュコロンビア州公衆衛生局（PH）への報告が求められ，2002 年 8 月より，その規制が施行された。本調査では，規制施行後 2 年半の TT-HCV 感染疑い例の増加数を調査するとともに，感染レシピエントにおける遡及（LB）調査及び感染ドナーにおける追跡（TB）調査の有効性を検討した。LB 調査は TB 調査により感染ドナーが特定された後に開始し，TB 調査は LB 調査により感染レシピエントが特定された後に開始した。PH への報告を介して特定された因果関係の否定できない TT-HCV 感染は 1%未満であることがわかった。全調査の 92%は 1992 年の第 2 世代抗 HCV 酵素免疫測定法によるドナースクリーニングを導入する前の輸血に関与していた。レトロスペクティブに TT-HCV 感染を特定するにあたって，スクリーニング導入日以降の輸血に対する LB 及び TB 調査実施の有益性はわずかであると考えられる。一方，HCV に感染したヒトの約 30%が LB 又は TB 調査の結果により，初めて自身の HCV の罹患状況を知ることとなった。結論として，現在の TT-HCV 感染疑いの報告手順では，その後の LB 調査又は TB 調査の開始までに長期間を要することが判明した。

**使用上の注意記載状況・その他参考事項等**

BYL-2007-0292

| 報告企業の意見 | 今後の対応 |
|---|---|
| 本文献は，PH に報告される輸血を介した HCV 感染の疑いのある症例の現在の報告手順は効果がないということを明確に示唆している。対照的に，感染者数の確認には，第 2 世代抗 HCV 酵素免疫測定法によるドナースクリーニングの導入が極めて効果的である。HCV に対する NAT スクリーニングは，弊社の血漿分画製剤，コージネイト FS 又はコージネイト FS バイオセットの製造工程培地に使用されている血漿分画成分の製造工程における血漿プールで，体系的に実施されている。 | 現時点で新たな安全対策上の措置を講じる必要はないと考える。 |

# Evaluating the impact of public health notification of suspected transfusion-transmissible hepatitis C virus infection and effectiveness of lookback and traceback investigations by Canadian Blood Services in British Columbia, Canada, August 2002 through February 2005

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**BACKGROUND:** Suspected transfusion-transmissible infections (TTIs) have been reported to public health (PH) in British Columbia (BC) since August 2002. The impact of PH notification of suspected transfusion-transmissible hepatitis C virus (TT-HCV) infection over the first 2.5 years and the effectiveness of HCV lookback (LB) and traceback (TB) investigations conducted by Canadian Blood Services (CBS) in BC were evaluated.

**STUDY DESIGN AND METHODS:** Suspected TT-HCV cases reported to CBS in BC between August 28, 2002, and February 28, 2005, were analyzed. The incremental yield of plausible TTIs from PH-reported suspected TTIs was calculated. The effectiveness of LB and TB investigations was assessed with respect to the impact of improved anti-HCV donor screening, the number of newly recognized HCV infections, and the timeliness of initiating investigations.

**RESULTS:** Nine of 553 (1.6%) investigations were initiated after PH reporting, yielding an additional 2 of 237 (i.e., 0.8%) plausible TTIs. Ninety-two percent of investigations with transfused units involved transfusions before implementing second-generation anti-HCV enzyme immunoassay (EIA) donor screening. Almost one-third of HCV-infected persons in linked investigations (i.e., LB triggered by a TB and vice versa) were newly identified. Recently tested, PH-reported cases incurred a mean delay exceeding 6 months until initiating a LB or TB investigation.

**CONCLUSION:** PH reporting of TTIs and investigating transfusions after second-generation anti-HCV EIA donor screening identified few plausible TT-HCV infections. Many HCV-infected recipients or lapsed donors first became aware of their infection status as a result of CBS investigations. The current process of reporting suspected TTIs incurs significant time delay.

Hepatitis C virus (HCV) disease has been notifiable to public health (PH) in British Columbia (BC) since 1992 and since then, more than 55,000 cases have been reported (J.A. Buxton, BC Center for Disease Control, personal communication, December 2006). In many instances, epidemiologic follow-up information is lacking, resulting in underrecognition of suspected transfusion transmissible HCV infection (TT-HCV) to blood suppliers. Even when recognized, suspected TT-HCV may be inconsistently reported to agencies such as blood suppliers for further investigation. Therefore, a regulatory requirement to notify PH of suspected TTIs might be expected to increase the sensitivity of TT-HCV case detection through lookback (LB; i.e., notifying and testing recipients of potentially contaminated blood) or, reciprocally, traceback (TB) investigations

In 2000, suspected TTIs, including suspected TT-HCV, were made reportable to PH in BC under the provincial Health Act.[1] The regulatory change was implemented in

**ABBREVIATIONS:** CBS = Canadian Blood Services; LB = lookback; PH = public health; TB = traceback; TT-HCV = transfusion-transmissible hepatitis C virus; TTI(s) = transfusion-transmissible infection(s).

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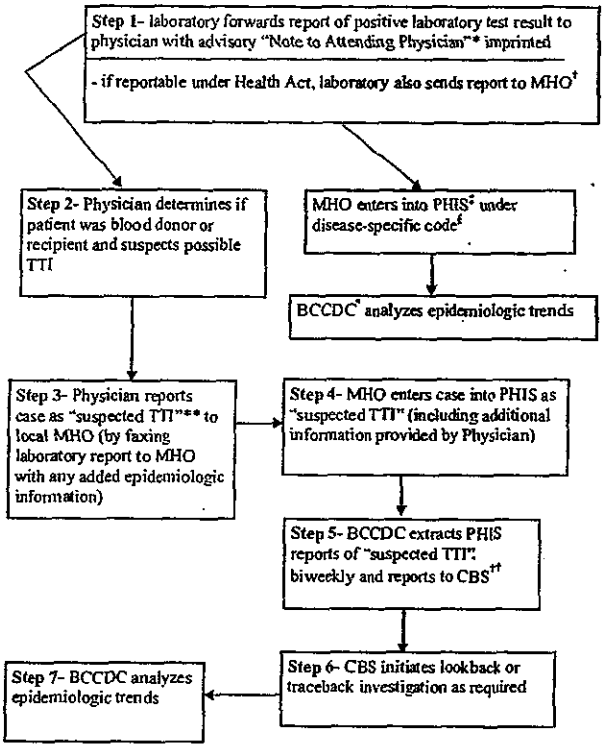


**Fig. 1. Procedure in BC for reporting and investigating suspected TTIs. *Note to attending physician—a standardized advisory note printed on all laboratory reports with a positive laboratory test result for specified blood-borne pathogens, advising physician to report as suspected TTI if patient has donated or received blood. †MHO = Medical Health Officer; ‡PHIS = Public Health Information System (electronic provincial case registry for diseases reportable to PH); §disease-specific code, for example, HCV, HBV; ¶BCCDC = British Columbia Center for Disease Control (provincial PH laboratory); **TTI = transfusion transmissible infection; ††CBS = Canadian Blood Services.**

August 2002, at which time reporting of suspect TTIs to PH began.[1] A suspected TTI was defined as a laboratory-confirmed, blood-borne infection diagnosed in a recipient of blood or blood products which, in their doctor's assessment, was likely transfusion transmitted.[2] Newly diagnosed cases of a blood-borne infection in a former blood donor were also included in the new reporting provisions. To our knowledge, BC is the first jurisdiction in the world to legally mandate reporting of suspected TTIs to PH. PH in turn forwards reports to Canadian Blood Services (CBS). In BC, CBS is responsible for coordinating and conducting all LB and TB investigations. The current procedure in BC for reporting suspected TTIs is shown in Fig. 1.

One objective of this statutory requirement for reporting suspected TTIs was to improve surveillance of the risk of TTIs such as TT-HCV.[2] Blood suppliers in Canada, the United States, and other countries, however, as well as hospitals in some jurisdictions, had already implemented targeted HCV LB and TB programs.[3-9] Evaluations of both general and targeted HCV LB investigations have reported relatively low yield in identifying HCV infected recipients.[8-15] A recent review of the Canadian experience with targeted HCV LB investigations[16] highlighted a trend, previously reported,[17-20] of further decreasing yield of such investigations since implementing increasingly sensitive serologic (i.e., second-generation[21] and later anti-HCV assays[22,23]) and nucleic acid–based[24,25] donor screening.

In this study, our primary objective was to quantify the incremental yield of identified TT-HCV infections, 2.5 years after implementing the regulatory requirement in BC to report cases of suspected TT-HCV to PH. Two secondary objectives were, first, to assess the effectiveness of HCV LB and TB investigations, not only in identifying previously unrecognized TT-HCV infections, but also in light of increasingly sensitive HCV donor screening, starting with implementation of second-generation anti-HCV assays, and second, to assess the timeliness of the current reporting process for suspected TTIs.

## MATERIALS AND METHODS

Data from all cases of suspected TT-HCV (including co-infections with HCV and one or more other blood-borne pathogens) reported to CBS in BC, from August 28, 2002, to February 28, 2005, were entered into a computer database (Access, Microsoft Corp., Bellevue, WA) and imported into another computer program (Excel, Microsoft Corp.) for descriptive analyses. Cases were categorized as either "PH-reported" (i.e., reported to CBS through the new regulatory process for PH reporting of suspected TTIs) or as "non–PH-reported" (i.e., reported directly to CBS from all other sources, including physicians, hospitals, donors, or recipients). TT-HCV comprised 97 percent of all suspected TTI cases reported to CBS over this period. Outcome data from ensuing HCV LB and TB investigations were analyzed, including donor and recipient HCV test assay (e.g., enzyme immunoassay [EIA] or nucleic acid test), test date, and test result.

The plausibility of TT-HCV infections was determined according to an appropriate chronology of donor and recipient test results. Plausible TT-HCV infection was discounted in two circumstances: a positive recipient HCV test result before the date of transfusion in question in a HCV LB and, as specified by CBS procedures, a negative donor anti-HCV (second generation or later anti-HCV assay) test result from a specimen collected at least 140 days after the donation date of the transfusion in question (which cleared the donor from a HCV TB investigation). The impact of implementing PH reporting of

suspected TT-HCV infections was measured by comparing the yield of plausible TT-HCV infections from LB and TB investigations initiated as a result of PH-reported and non–PH-reported cases.

To gauge the impact of increasingly sensitive donor HCV testing, the proportions of HCV-infected donors and recipients identified in TB and LB investigations, respectively, were calculated for transfusions occurring before, compared with after implementing second generation anti-HCV donor screening. Second-generation anti-HCV EIA (Ortho Diagnostic Systems, Raritan, NJ) blood donor screening was implemented in Canada in March 1992.

To estimate the number of HCV infections in donors and recipients which was first recognized as a result of these investigations, we examined the outcomes of "linked" LB (i.e., an anti-HCV–positive donor first identified through a TB investigation) and "linked" TB investigations (i.e., an anti-HCV–positive recipient first identified through a LB investigation). For linked LB investigations, we examined the time from a donor's positive test result to the opening date of a LB investigation. If this time period was less than 100 days, then it was considered likely that the donor became aware of their infection status through CBS notification. Analogously, for linked TB investigations, we examined the time from a recipient's positive test result to the opening of a TB investigation as an indirect means of assessing whether a recipient likely became aware of their infection status through CBS notification.

To assess the timeliness of the current process for reporting suspected TTIs, we calculated the mean number of days from a positive HCV test result for a donor or recipient, to the opening of a LB or TB investigation, respectively, for PH-reported and non–PH-reported cases.

## RESULTS

### Yield of plausible TT-HCV infections from LB and TB investigations

During the study period, 31 suspected TT-HCV cases (including 2 cases with a history of both donation and receipt of blood) were reported to CBS from PH. Nine investigations (5 LB and 4 TB) were initiated as a result of PH-reported cases (Table 1). Fourteen other investigations also involving PH-reported cases had already been initiated as a result of prior (i.e., duplicate) reporting of cases to CBS from other sources.

Two plausible TT-HCV infections (one each from LB and TB investigations) were identified as a result of cases exclusively reported to CBS by PH (Table 2). By comparison, 235 plausible TT-HCV infections (127 from LB and 108 from TB investigations) were identified through reports received by CBS from non-PH sources (including 14 cases involving duplicate reporting from PH).

**TABLE 1. Case reporting sources for HCV LB and TB investigations**

| | Case reporting source | | | |
|---|---|---|---|---|
| HCV investigation | PH | Non-PH | Duplicate* | Total |
| LB | 5 | 232 | 10 | 247 |
| TB | 4 | 298 | 4 | 306 |
| Total | 9 | 530 | 14 | 553 |

* Case reported from both PH and non-PH sources.

### Impact of second-generation anti-HCV EIA donor screening

A total of 122 of 128 (95.3%) HCV LB investigations with transfused units identified involved donations before second-generation anti-HCV EIA donor screening and 127 of 150 (84.7%) recipients from these earlier HCV LB investigations were anti-HCV–positive (Table 3). In contrast, only one anti-HCV–positive recipient was identified who was transfused after this time, and this recipient had also received 4 units implicated in HCV LB investigations before second-generation anti-HCV EIA donor screening. Similarly, for HCV TB investigations with transfused units identified, 153 of 171 (89.4%) involved donations before second-generation anti-HCV EIA donor screening. One hundred twenty-three of 406 (30.3%) donors from these earlier HCV TB investigations were anti-HCV positive, compared with none after this time.

### Identifying previously unrecognized HCV infection

Eighty-five of 247 (34.4%) HCV LB investigations were initiated after identifying an infected donor through a TB investigation. Follow-up test results were available for 77 of these 85 donors, of whom 29 (37.7%) first learned of their HCV disease status as a result of the TB investigation (data not shown). Ninety-five of 307 (30.9%) HCV-TB investigations were initiated after identifying an infected recipient through a LB investigation, of whom 26 recipients (27.4%) first learned of their HCV disease status as a result of the LB investigation (data not shown).

### Timeliness of initiating HCV LB and TB investigations

The overall mean number of days from a donor positive test result to initiation of a LB or TB investigation for both exclusively PH or non–PH-reported cases was similar and protracted—greater than 6 months (Table 4). The mean interval was reduced to 39.5 days after discounting one significant outlier among the five PH-prompted LB investigations (data not shown). Similarly, discounting one outlier among the four TB investigations involving PH-reported cases reduced the mean interval to 161 days (data not shown).

**TABLE 2. Plausible TT-HCV infections identified through LB and TB investigations**

| Investigations | Case reporting source: PH | Non-PH (including duplicate*) reported | Total |
|---|---|---|---|
| HCV LB | | | |
| Investigations with transfused units | 1 | 127 | 128 |
| Units with recipient HCV test result available | 1 | 155 | 156 |
| Plausible TT-HCV infections | 1 | 127 | 128 |
| HCV TB | | | |
| Investigations with transfused units | 1 | 170 | 171 |
| Units with donor HCV test result available | 1 | 529 | 530 |
| Plausible TT-HCV infections | 1 | 108 | 109 |

* Case reported from both PH and non-PH sources.

**TABLE 3. Relative yield of TB and LB investigations before and/or after second-generation anti-HCV EIA donor screening**

| Investigations | Transfusion date: Before second-generation anti-HCV EIA | After second-generation anti-HCV EIA | Total |
|---|---|---|---|
| HCV LB | | | |
| Investigations with transfused units | 122 | 7 | 129* |
| Number of available recipient HCV test results | 150 | 6 | 156 |
| Number of anti-HCV–positive recipients | 127 | 1† | 128 |
| HCV TB | | | |
| Investigations with transfused units | 153 | 23 | 176‡ |
| Number of available donor HCV test results | 406 | 124 | 530 |
| Number of anti-HCV–positive donors | 123 | 0 | 123 |

* One HCV LB investigation involved donations before and after second-generation anti-HCV EIA testing.
† Recipient received 5 units involved in HCV LB investigations, 4 of which were transfused before second-generation anti-HCV EIA testing.
‡ Five recipients received units both before and after second-generation anti-HCV EIA testing.

## DISCUSSION

In the first 30 months since implementing TTI reporting in BC, 9 HCV LB or TB investigations were initiated following suspected TT-HCV cases reported exclusively by PH, comprising 1.6 percent of the 553 investigations that were opened during this period. From these 9 investigations, an additional two plausible TTIs were identified, representing an incremental yield of less than 1 percent (2 of 237) of plausible TTIs identified. Because unexplored alternative epidemiologic risk factors in these cases may also be more relevant, this analysis clearly indicates limited incremental benefit attributable to PH notification of suspected TTIs in BC.

Increasingly sensitive donor screening of HCV infection[17,21-25] has substantially reduced the risk of TTI-HCV.[11,16,18,19] In this study, 92 percent (275 of 299 [excluding 6 investigations involving one donor and five recipients who, respectively, donated or received units both before and after implementing second-generation anti-HCV EIA donor screening]) of LB and TB investigations (with transfused units) involved transfusions before implementing second-generation anti-HCV EIA donor screening in 1992 (Table 3). For transfusions since 1992, the incremental benefit of LB or TB investigations in identifying previously unrecognized TT-HCV appears marginal and supports the call by others[15,16,20] for a review of the medical, ethical, political, and legal rationale for undertaking such investigations involving recently transfused units.

In contrast, our evaluation of the PH impact of transmissible disease notification through LB and TB investigations identified a significant number of HCV-infected recipients and past donors who were likely unaware of their disease status. Over one-quarter (27.4%) of anti-HCV–positive recipients in LB investigations linked to a prior TB investigation first became aware of their infection through CBS notification, whereas for anti-HCV–positive donors in TB investigations linked to a prior LB investigation the corresponding proportion was 37.7 percent. This is somewhat lower than the range (42%-68%) of newly identified HCV infections from general or targeted HCV LB investigations reported from earlier investigations undertaken in Canada and the United States[3,4,6,10,11] and could reflect a diminishing proportion of cases associated with transfusions before the advent of donor anti-HCV testing. As pointed out by AuBuchon,[15] however, the health benefit of earlier detection of TT-HCV is likely mitigated by the reduced cost-effectiveness (i.e., cost per life-year gained) of HCV treatment for many HCV-infected blood recipients, given a mean transfusion recipient age of 60 to 65 years.[26] With passing time, it can be confidently predicted that HCV LB and TB investigations will detect an ever-decreasing proportion of previously unrecognized HCV infection.

This study identified prolonged intervals between the date of a positive laboratory test result in a blood donor or recipient and opening of an appropriate LB or TB investigation. Minimizing these times may enable potentially

**TABLE 4. Interval (days) between positive HCV test result and initiation of HCV LB or TB investigation**

| | Days from positive HCV test result to initiating HCV LB or TB investigation | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PH reported cases | | | | Non-PH (including duplicate*) reported cases | | | |
| Investigations | Number | Mean | Median | Range | Number | Mean | Median | Range |
| HCV LB | 5 | 232 | 52 | 2-1004 | 232 | 799 | 89 | 2-4353 |
| HCV TB | 4 | 321 | 221 | 41-801 | 296 | 1427 | 1020 | 7-4880 |

* Case reported from both PH and non-PH sources.

infectious in-date blood products—primarily fresh-frozen plasma—to be withdrawn from inventory sooner. Although it appears that PH-reported cases were investigated sooner, this is largely an artifact of different time periods for laboratory test dates between PH and non-PH cases. All investigations of PH-reported cases during the study period were as a result of laboratory testing that had been performed between 2000 and 2005, whereas investigation of non–PH-reported cases that were initiated during the study period had laboratory testing performed as far back as 1990.

Measures have been implemented in BC to reduce the reporting delay of suspected TTIs, such as establishing a provincial Central Transfusion Registry in 1998. The current process for reporting suspect TT-HCV continues, however, to incur prolonged delay for several reasons. First, prior donation or transfusion history may be inconsistently or unreliably recalled.[9,27-29] Second, infections with reporting case definitions that require manual integration of both laboratory and clinical data are more likely to be underreported and reported in a less timely fashion than routine, automated electronic laboratory reporting of positive laboratory results.[27-31] To improve the efficiency of identifying and reporting suspected TTIs to CBS, an automated, anonymized data linkage process between the provincial PH laboratory at BCCDC, CBS, and the provincial Central Transfusion Registry, is currently being evaluated.[32]

In summary, less than 1 percent of plausible TT-HCV cases were identified exclusively through PH reporting, along with a similar low yield of infected cases identified from investigations involving transfusions after second generation anti-HCV donor screening. Overall, approximately one in three suspected TT-HCV infections identified by LB or TB investigations was a newly detected infection. This case detection benefit will diminish in tandem with the decreasing future number of HCV LB and TB investigations involving transfusions before donor second generation anti-HCV donor screening. The current process of identifying and reporting suspect TT-HCV infections incurs delays in initiating follow-up LB or TB investigations.

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# 医薬品 研究報告 調査報告書

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| 一般的名称 | 新鮮凍結人血漿 | 研究報告の公表状況 | Seeley WW, Marty FM, Holmes TM, Upchurch K, Soiffer RJ, Antin JH, Baden LR, Bromfield EB. Neurology. 2007 Jul 10;69(2):156-65. | 公表国 |
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**研究報告の概要**

○移植後急性大脳辺縁系脳炎:臨床特性およびHHV6との関連性
背景:治療関連免疫抑制時においてヒトヘルペスウイルス6(HHV6)に起因すると考えられる急性大脳辺縁系脳炎が報告されている。しかし、この症候の臨床特性及び臨床検査特性はよく分かっていない。
方法:同種造血幹細胞移植(HSCT)後に急性大脳辺縁系脳炎を発症した患者9名の臨床特性、EEG、MRI、ならびに臨床検査特性を報告する。HHV6と本症候との関係性を調べるため、2003年3月17日～2005年3月31日までに当センターの診察を受けたHSCT患者全員から入手することのできたCSFのPCRによるHHV6検査結果を調べた。
結果:患者は、順行性健忘、不適切な抗利尿ホルモン分泌症候群、軽度CSF細胞増加症、一時的なEEG異常(顕性、不顕性けいれん発作を反映する場合が多い)を特徴とする、一定的で特徴的な臨床症候を示した。MRIでは、T2、FLAIR、DWI画像にて、鉤、扁桃体、内側嗅領、海馬領域内に高信号域を認めた。PCRを用いた初回腰椎穿刺CSFの検査では9名中6名がHHV6陽性であった。患者はいずれもfoscarnetまたはganciclovirによる治療を受けた。長期生存者の認知機能回復には、ばらつきがあった。1名の脳剖検では、大脳辺縁系グリオーシス及び扁桃体と海馬における著しい神経細胞脱落が示された。HHV6 CSF検査を2年間行ったHSCT患者27名のうち、臨床的大脳辺縁系脳炎を発症した患者にのみ陽性結果を認めた。
結論:同種造血幹細胞移植を行う患者には、神経症候の特徴的な移植後急性大脳辺縁系脳炎(PALE)のリスクがある。治療の検討には、積極的な発作管理と(場合によっては)抗ウイルス療法を含めるべきである。PALEは、CSF中のヒトヘルペスウイルス-6と関連付けられる可能性があるが、当該ウイルスの病原的役割についてはさらに検討が必要である。

| 報告企業の意見 | 今後の対応 |
|---|---|
| 同種造血幹細胞移植後に急性大脳辺縁系脳炎を発症した患者9名中6名が初回腰椎穿刺CSF検査でHHV6陽性となり、急性大脳辺縁系脳炎がCSF中のHHV6と関連付けられる可能性が示されたとの報告である。 | 今後も情報の収集に努める。 |

**使用上の注意記載状況・その他参考事項等**

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク