F13-B is composed of 641 amino acid residues. F13-B consists of 10 tandem repeats that have been designated as Sushi domains, or short consensus repeats (SCRs). At least 3 of the 10 Sushi domains of F13-B have distinct functions to form either a homodimer or a heterotetramer with F13-A. The gene of F13-B is composed of 12 exons, and each sushi domain is coded by a single exon. The Human Genome Project has identified homologous Sushi domains in a total of 53 genes. Nuclear magnetic resonance studies revealed that Sushi domains in complement factor H consist of double- or triple-stranded β-sheets and several β-turns and cuboid forms.

Although tissue TGase exists in most tissues and organs, F13-A is mainly limited to plasma and megakaryocytes/platelets and monocytes/macrophages, and placenta in pregnant females. The site of synthesis for F13-B is the liver.

F13 is a proenzyme converted to an active enzyme called F13a by thrombin that is generated in the final stage of the blood coagulation cascade. F13 plays an important role or roles in hemostasis, wound healing, and maintenance of pregnancy. The enzyme promotes clot stability by forming covalent bonds between fibrin molecules and also by crosslinking fibrin with several proteins including α_2-plasmin inhibitor (α_2-PI) and fibronectin. These reactions lead to an increase in the mechanical strength, elasticity, and resistance to degradation by plasmin of fibrin clots, and promotion of wound healing by providing a scaffold for fibroblasts to proliferate and spread. It is suggested that interactions of F13 with other cells such as macrophages and platelets play important roles in the physiological reactions.[8,9]

CLASSIFICATION OF F13 DEFICIENCY

The normal range of plasma F13 levels is generally 70 to 130%. Thus individuals with levels <70% are F13 deficient, subclassified into congenital and acquired types (Table 1). The former is caused by defects in either the F13-A or F13-B gene,[10] and the latter is caused by a secondary F13 reduction mainly due to hyposynthesis and/or hyperconsumption through a primary disease, such as leukemia, myelodysplastic syndrome and liver diseases, disseminated intravascular coagulation (DIC), major surgery, or chronic inflammatory bowel diseases. F13 deficiency should also be subclassified into hemorrhagic (symptomatic) and nonhemorrhagic (asymptomatic/laboratory) categories. It used to be described that as low as 5% of plasma F13 activity is sufficient for normal hemostasis from observations in congenital F13 deficiency. However, the F13 level to delineate the boundary between hemostasis and hemorrhage could be much higher and became more controversial in both congenital and acquired settings.[11–13]

Table 1 Classification of Factor 13 Deficiency

A. Congenital factor (F)13 deficiency
1. Congenital F13-A deficiency
2. Congenital F13-B deficiency
3. Congenital combined F13-A and F13-B deficiency (not found)
B. Acquired F13 deficiency
1. Hemorrhagic (symptomatic) acquired F13 deficiency (including acquired hemorrhaphilia 13)
anti-F13 autoantibody (type I, neutralizing type; type II, binding type)
other F13 inhibitors (paraprotein, etc.)
severe secondary F13 deficiency (DIC, surgery, trauma, liver diseases, leukemia, etc.)
idiopathic/cryptogenic
2. Nonhemorrhagic (asymptomatic or laboratory) acquired F13 deficiency mild secondary F13 deficiency (DIC, surgery, trauma, liver diseases, leukemia, etc.)
C. Acquired hemophilia 13-like diseases (acquired dysfunction of F13-related molecules)
1. Autoantibodies against F13 substrates (fibrinogen, α_2-PI, etc.)
2. Inhibitors against F13 substrates (fibrinogen, α_2-PI, etc.)
D. Artifacts
1. Sample errors (serum, mislabeling with normal plasma)
2. Consumption of F13 in samples (clotting by inappropriate blood collection)
3. Inactivation of F13 in samples (long-term storage under inappropriate conditions)
4. Lack of reagents (calcium, thrombin, etc.)

DIC, disseminated intravascular coagulation; α_2PI, α_2-plasmin inhibitor.

CONGENITAL F13 DEFICIENCY

About 500 cases of congenital F13 deficiency have been identified, and its prevalence is reported to be one in 2 million. A lifelong bleeding tendency, as well as abnormal wound healing and recurrent miscarriage, are common symptoms of congenital F13 deficiency. The first manifestation is mostly umbilical bleeding within several days after birth, and the most common cause of death is intracranial bleeding. Oozing and after bleeding are also characteristic of congenital F13 deficiency because a once-formed hemostatic clot is easily lysed after a half day or 1 day in these patients.

We classified congenital F13 deficiency at the genetic DNA level: F13-A deficiency (former type II deficiency) and F13-B deficiency (former type I deficiency), and a possible combined deficiency of F13-A and F13-B[10] (Table 1; http://www.med.unc.edu/isth/99FXIII.html). Because the genes for F13-A and F13-B are localized to chromosomes 6p and 1q, respectively, F13 deficiency is inherited as an autosomal recessive trait and caused by the absence of either subunit. However, heterozygotes of these deficiencies may manifest a mild bleeding tendency.[11,14]

Most of congenital F13 deficiencies are caused by defects in the *F13-A* gene whose mutations are highly heterogeneous, including a variety of missense and nonsense mutations, small deletions and insertions with or without out-of-frame shift/premature termination and splicing abnormalities. Most recently, it was reported that F13-B deficiency is not uncommon, at least in the German white population.[14]

ACQUIRED HEMOPHILIA 13

Epidemiology

In Japan, an increasing number of otherwise healthy subjects suddenly manifested severe bleeding symptoms in the absence of family history or prolonged clotting times. When we performed a nationwide study by sending a questionnaire to ~1800 hospitals, 59 suspicious cases were found; 11 and 8 cases had mildly (<40% and <70%) and severely (<40%) decreased F13 activity, respectively. During 5 months in the late 2009, 18 candidates were consulted, and the selected 10 cases were diagnosed with AH13 or HAF13def. Thus the incidence was estimated to be 2 cases/month or 24 cases/year in Japan. However, in Kitakyushu City with a population of 1 million, one case of AH13/HAF13def has been diagnosed every year; therefore 120 people per year may develop this disease in Japan, and 80% (96 cases) may be overlooked because of the lack of an efficient routine screening test for F13 deficiency. This number, one case/million per year, is the same as the incidence of AHA.[2,3]

It is noteworthy that two definite AH13 cases were found in each of three cities with populations of 120,000, 390,000, and 480,000, respectively, within short intervals. It is very likely that a physician who has diagnosed a patient with AH13 case once will easily find another case, whereas a physician who has never seen such patients may be prone to overlook them. Accordingly, we have sent flyers describing this disease and are delivering seminars/lectures and publishing review articles.

Pathophysiology

As mentioned earlier, HAF13def includes both hemorrhagic acquired F13 deficiency with inhibitors (AH13) and one without F13 inhibitors (simple HAF13def; Table 1; Fig. 1). A literature search using PubMed found two Japanese case reports of F13 inhibitors (i.e., AH13). Another search using the Igaku Chuo Zasshi system (a database for medical journals in Japanese) found 15 HAF13def cases; 7 of these were AH13.

In our hands, 16 cases were diagnosed as HAF13-def by mid-2009, and 7 of them had anti-F13 antibodies (i.e., AH13). During our nationwide study in late 2009 and early 2010, 5 among 20 cases with HAF13def were confirmed to have anti-F13 antibodies. Accordingly, at least 21 Japanese cases, mostly in the elderly, had developed F13 inhibitors; this number is similar to that summarized by Lorand and Egbring et al using publications between 1967 and 1992, a period of 25 years.[4,5] Because relatively few articles have been published so far this century,[15] such case reports may not be accepted by major medical journals. Patients with AH13 may be more prevalent in Japan than in other countries for some reason. About half of them had no underlying diseases; the remaining half had autoimmune diseases, cancers, and so on. Previously, it was also reported that AH13 would occur in patients with autoimmune diseases, malignancies, and drug-induced disorders.[4,5] All of our 12 cases had immunoglobulin-type inhibitors. However, other type inhibitors, like paraproteins, may exist among the remaining cases of HAF13def tentatively labeled as "without anti-F13 inhibitors" because we have not detected them by specific assays.

Among 7 and 15 cases diagnosed as simple HAF13def before and during the domestic study, respectively, most patients had suffered from diseases such as atypical Henoch-Schönlein purpura, uncreative colitis, abdominal aortic aneurysm, myelodyscrasia, cancers, chronic hepatitis C, or interstitial pneumonia. The remaining patients had no underlying diseases despite severe bleeding symptoms.

Laboratory Tests and Diagnosis (Table 2)

There is neither a past history nor family history of bleeding tendency in the patients with AH13/HAF13def. Severe bleeding mainly occurs in soft tissues, such as skin and muscle, but it can occur anywhere in the body, even in the various cavities. Intracranial, intrathoracic including cardiac tamponade, and intra-/retroperitoneal bleeding are life threatening and need to be treated immediately. Continuing bleeding and oozing-type bleeding are also indicative signs of AH13/HAF13def. Patients with AH13/HAF13def frequently present progressing severe anemia and sometimes shock because of an acute massive blood loss. Regular clinical reviews supported by measurement of hemoglobin or hematocrit level are crucial for optimal outcomes.

When routine general screening tests for bleeding tendencies, such as activated partial thromboplastin time and prothrombin time, platelet counts, and aggregation tests are normal or near-normal ranges in a suspected patient, physicians should consider AH13/HAF13def. The measurement of F13 activity is not sufficient but definitely required for the specific screening of F13-deficient conditions. One must pay attention to the fact that all the ordinary methods typically employed

do not measure the functional enzymatic F13 activity toward any physiological macromolecular substrates, such as fibrin and α_2-PI, whose crosslinking is essential for normal hemostasis. One must also remember that the F13 activity value measured by the ammonium release assay contains a high background of ~10%, as confirmed previously.[16]

We used the following tests for the screening and confirmatory tests of AH13 (Table 2): an ammonium release assay for F13 activity after incubation of samples at 37°C for 2 hours: (a) patient plasma, (b) control plasma, and (c) 1:1 mixture of normal and control plasma. If the value of (c) is less than the average of (a) and (b), one should suspect the presence of F13 inhibitors. Once suspected, we must try to detect F13 inhibitors in the patient's plasma by a five-step dilution mixing assay by amine incorporation, and an immunoblot test and/or enzyme-linked immunosorbent assay for antibodies against F13-A, F13-B, and A_2B_2 complex (Souri and Ichinose, manuscript in preparation). When F13 activity of normal control plasma is nearly completely inhibited by the addition of patient's plasma, it is classified as a type I (neutralizing type) inhibitor. When F13 of normal plasma is only partially inhibited and the presence of F13 and inhibitor complex is confirmed, it is classified as a type II (binding type) inhibitor. Even if F13 activity against small synthetic substrates was within a normal range, its activity toward fibrin must be examined by the crosslinking of fibrin by sodium dodecyl sulfate-polyacrylamide gel electrophoresis in order not to overlook such types of inhibitors. In our hands, the immunological detection of inhibitors employing a dot blotting method has been the most sensitive and successful because both type I and type II antibodies bind to F13 antigens. The difference in α_2-PI levels between patient's plasma and serum is also a relatively good indicator of F13 function (Ichinose et al, manuscript in preparation).

In vivo recovery test of F13 is also useful and practical. One can estimate at least the pharmaceutical efficacy of F13 replacement therapy and at the same time its clinical efficacy.

When any of the confirmatory tests just described were negative, patients were considered to have simple HAF13def, without anti-F13 inhibitors (Fig. 1). However, this diagnosis is only tentative, as described earlier. Possible antibodies against α_2-PI or fibrin/fibrinogen were also not examined.

Management

It is most important to stop bleeding immediately by injecting F13 products whenever possible. Plasma-derived F13 concentrates contain ~240 units/vial and are currently available in Japan and in most European countries. Cryoprecipitate and fresh-frozen plasma are

Table 2 Tests for Acquired Hemorrhaphilia 13/Hemorrhagic Acquired Factor 13 Deficiency

A. Eligibility (inclusive) criteria
  1. aPTT, platelet count, and aggregation tests: normal or subnormal range
  2. Past history and family history of bleeding tendency: absent
  3. Specific causes for bleeding: absent
B. Screening tests
  1. Plasma F13 activity
    a. Patient's F13 activity after 2-hour incubation at 37°C: <50%
    b. Control's F13 activity after 2-hour incubation at 37°C: nearly 100%
    c. 1:1 mixing test for F13 activity after 2-hour incubation at 37°C: lower than (a + b)/2, to be examined further
  2. α_2-PI activity
    a. Plasma α_2-PI activity: nearly 100%
    b. Serum α_2-PI activity ~80% of the plasma value: when close to the plasma value, to be examined further
  3. FDP: if >5 μg/mL, to be examined further
  4. D-dimer: when disproportionally low compared with the FDP value, to be examined further
C. Negative tests for exclusion
  1. Plasma FVIII activity: near 100%
  2. Plasma FIX activity: near 100%
D. Confirmatory tests
  1. Five-step dilution mixing test for F13 activity between patient's and normal plasmas
  2. ELISA for F13-A and F13-B antigen levels
  3. Western blotting for F13-A and F13-B proteins
  4. Fibrin crosslinking test by SDS-PAGE
  5. Dot blotting and ELISA for anti-F13-A and anti-F13-B inhibitors using an antihuman Ab to IgG, IgM, and IgA classes
  6. Dot blotting and ELISA for anti-fibrin/fibrinogen and anti-α_2-PI inhibitors, etc.

aPTT, activated partial thromboplastin time; FDP, fibrinogen degradation product; ELISA, enzyme-linked immunosorbent assay; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; Ig, immunoglobulin.

other sources of F13, although they contain only ~3 and 1 unit/mL of F13, respectively.[17] Thus one must pay attention to possible circulatory overload by the F13 replacement therapy for hemostasis. There is no clear rule how much F13 should be infused; however, as a rule of thumb, the more severe the symptoms, the higher the F13 dose should be administered (e.g., up to nearly 100% for life-threatening intracranial bleeding). However, there is a limit for F13 replacement therapy in Japan regulated by social insurance (i.e., 1440 units per day for 5 days).

Antifibrinolytic therapy employing tranexamic acid or aprotinin may be partly effective to protect a hemostatic clot from the fibrinolytic activity of plasmin, especially when there are difficulties in the administration of F13. However, one should keep in mind that F13 has at least two major hemostatic functions (i.e., fibrin stabilization and antifibrinolysis); tranexamic acid and aprotinin only have an effect on the latter. Therefore, the effect of antifibrinolytic agents alone may be limited and not sufficient to stop severe bleeding.

When a patient with HAF13def has an F13 inhibitor (i.e., an AH13 case), immunosuppressive therapy has to be initiated as soon as possible. Corticosteroid is usually the first-line medicine and cyclophosphamide the second. The inhibitors tend to decrease after 3 to 4 weeks and normally disappear after ~2 months. When both drugs fail, a combination of these two is worth a try. Rituximab can be also the next choice, although it is not currently approved by social insurance at least in Japan. An anti-F13 inhibitor in a patient spontaneously disappeared without specific immunosuppressant therapy after several years.[18] This patient had been at risk of bleeding for a long time.

Finally, severe anemia needs be taken care of by a transfusion of fresh blood or red cell concentrates.

Secondary F13 Deficiency

Acquired F13 deficiency (Table 1) is frequently found secondary to various disease states, such as DIC and surgery due to enhanced consumption of F13, and leukemia and hepatic disorders because of the impaired synthesis of F13-A and F13-B, respectively.[12,13,19,20] The decreased F13 levels may contribute to the bleeding tendencies of these diseases in cooperation with global reduction in other clotting factors and/or platelets. However, it is uncertain whether or not one should administer F13 products, even if F13 activity was significantly reduced in these conditions.

F13 decreases in the plasma of patients with chronic inflammatory bowel diseases, and F13 replacement therapy has been reported to be useful. It is very likely that F13 is consumed in the inflammatory intestine, which in turn results in impaired wound healing and continuous bleeding in the damaged tissue. F13 is also known to decrease in patients with Henoch-Schönlein purpura, especially with abdominal complications. In such cases, the administration of F13 concentrates often leads to good control of the disease.[20] The mechanism or mechanisms of this F13 reduction is not known at present.

Perspective

At the moment, there are 13 major and minor problems/questions with regard to the laboratory tests, diagnosis, and treatment of AH13/HAF13def (Table 3). Because we decided to perform the domestic nationwide survey in Japan 2 years in a row, the actual situation of AH13/HAF13def will at least be clarified there.[21] In addition, we have proposed an international collaborative study for AH13 at the annual International F13 Symposium in February 2010, in Nurenberg, Germany, and at the International Society on Thrombosis and Haemostasis/Scientific and Standardization Committee meeting in May 2010 in Cairo, Egypt.

Routine clotting time assays cannot find F13 deficiency, and ordinary clot solubility tests can detect only extremely low levels of F13.[22] However, we hope a new screening test based on the simple clot retraction reaction of platelet-rich plasma[9] will be developed soon (Yatomi and Ichinose, manuscript in preparation). The new method will be fast, simple, and ubiquitous.

At least some coagulation research centers in each country must be capable of performing the dot blot assays to sensitively detect anti-F13 antibodies, although

Table 3 13 Problems/Questions Regarding Acquired Hemophilia 13/Hemorrhagic Acquired Factor 13 Deficiency

1. The actual situation of AH13/HAF13def is unknown.
2. It cannot be found by routine clotting time assays.
3. There is no appropriate screening test for reduced F13 activity.
4. It is unpopular and time consuming to measure F13 activity or antigen.
5. It is difficult to detect inhibitors against F13.
6. Ordinary F13 activity assays cannot detect impaired crosslinking of its physiological macromolecular substrates, such as fibrinogen and α_2-PI.
7. It is unclear if reduced F13 is really responsible for bleeding.
8. Proper doses of F13 to stop bleeding are unknown.
9. It is uncertain whether or not F13 replacement really works to stop bleeding.
10. There is a limit on F13 dosing by the social insurance.
11. There is no bypassing alternative drug.
12. Rituximab for AH13 is not approved by Japanese social insurance.
13. The naming of AH13 has been controversial.

AH/HA13def, acquired hemorrhaphilia/hemorrhagic acquired F13 deficiency; α_2PI,α_2-plasmin inhibitor.

these are not ordinary tests. Such assays will become commercially available if the prevalence of AH13/HAF13def turns out to be much higher.

Our continuing trials to treat AH13/HAF13def patients with F13 products will elucidate the critical F13 levels for bleeding and hemostasis, and they will make it possible to estimate the proper dose of F13 products to control bleeding. When convincing results of our domestic study and those of possible international surveys are obtained, the Japanese insurance system may finally approve increased doses of F13 concentrates to stop ongoing bleeding in AH13 patients as well as the use of rituximab to eliminate anti-F13 autoantibodies.

In conclusion, we would ask clinicians to measure F13 activity whenever they see bleeding patients with no clear explanation.

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VI. 参考資料

原因不明の出血！

出血症状があるのに、ハッキリした原因が分らない患者さんを診たら?

後天性血友病XIII(13)※の可能性があります

※出血性後天性第XIII/13因子欠乏症の一部

特徴

1. 出血性素因の家族歴、既往歴のない患者さんで、
2. 原因不明の皮下出血、筋肉内出血、あるいは(開放創の)後出血(いったん止血した12～36時間後に再び出血する)があるか、
3. 血が滲み出るような、所謂ウージング様の出血が見られるとき、
4. 通常の止血療法の効果が見られないとき、

後天性血友病XIII(13)や出血性後天性第XIII/13因子欠乏症による出血である可能性があります。
(なお、血小板の減少や機能低下、PTやaPPTの延長を伴っている場合もあるので、御注意ください。)

原因

多くの症例では、自己の第XIII/13因子に対する抗体による中和、あるいは第XIII/13因子の『過剰な』消費や産生減少による低下などが基盤となっています。

診断

出血症状の原因が分らない症例で、第XIII/13因子活性が著しく低下していること。(ただし、第XIII/13因子活性が正常範囲であってもフィブリン架橋結合反応が障害されている場合もあり、自己抗体の有無を含め精査が必要です。)

治療

当面の出血対策:第XIII/13因子補充療法、(抗線溶療法)
インヒビターの産生阻止:免疫抑制療法、血漿交換 など
(インヒビターの有無で治療法が異なるので、御注意ください。)

全国調査中です。

後天性血友病XIII(13)疑いの患者さんに遭遇された場合は、研究班代表(山形大学・一瀬白帝)、あるいは最寄りの班員の方にご連絡／ご相談ください。(裏面に班員のリストがあります。)
日本血栓止血学会のホームページもご覧ください。(班研究の大まかな内容も記載されています。)

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後天性血友病XIII(13)研究班 研究代表者
一瀬 白帝

厚生労働科学研究費補助金（難治性疾患克服研究事業）

「後天性血友病XIII(13)の実態調査、発症機序の解明と治療方法の開発研究」班員の連絡先

（細い横線内は、分子病態、外科・救急、内科・小児科のサブグループのメンバーで、所在地によって北から南の順に記載した。）

研究代表者

一瀬 白帝	山形大学医学部 分子病態学	教　授	aichinos@med.id.yamagata-u.ac.jp

研究分担者

惣宇利 正善	山形大学医学部 分子病態学	講　師	msouri@med.id.yamagata-u.ac.jp
山本 正雅	奥羽大学薬学部 生化学	准教授	n-yamamoto@pha.ohu-u.ac.jp
坂田 洋一	自治医科大学 分子病態治療研究センター 分子病態研究部	教　授	yoisaka@jichi.ac.jp
矢冨　裕	東京大学医学部附属病院 検査部	教　授	yatoyuta-tky@umin.ac.jp
丸山 征郎	鹿児島大学大学院医歯学総合研究科 システム血栓制御学	特任教授	rinken@m3.kufm.kagoshima-u.ac.jp
小林 隆夫	浜松医療センター（産婦人科）	院　長	tkoba@hmedc.or.jp
村田 幸平	市立吹田市民病院 外科	主任部長	colon@mhp.suita.osaka.jp
家子 正裕	北海道医療大学歯学部 内科学	教　授	iekom@hoku-iryo-u.ac.jp
川杉 和夫	帝京大学医学部 血液学	准教授	kaz@med.teikyo-u.ac.jp
前田 美穂	日本医科大学 小児科	教　授	maeda@nms.ac.jp
花房 規男	東京大学医学部附属病院 血液浄化療法部	講　師	hanafusa-tky@umin.ac.jp
石田 文宏	信州大学医学部 内科学第二	准教授	fumishi@shinshu-u.ac.jp
和田 英夫	三重大学大学院医学系研究科 臨床医学検査	准教授	wadahide@clin.medic.mie-u.ac.jp
嶋　緑倫	奈良県立医科大学 小児科 血液凝固学	教　授	mshima@naramed-u.ac.jp

研究協力者

窓岩 清治	自治医科大学 分子病態治療研究センター 分子病態研究部	講　師	madochan@ms.jichi.ac.jp
北島　勲	富山大学大学院医学薬学研究部 臨床分子病態検査学	教　授	kitajima@med.u-toyama.ac.jp
高松 純樹	愛知県赤十字血液センター（血液学）	所　長	j-takamatsu@aichi.bc.jrc.or.jp
宮田 茂樹	国立循環器病研究センター 臨床検査科	医　長	smiyata@hsp.ncvc.go.jp
橋口 照人	鹿児島大学大学院医歯学総合研究科 血管代謝病態解析学	教　授	terutoha@m3.kufm.kagoshima-u.ac.jp
川前 金幸	山形大学医学部 麻酔科学	主任教授	kkawamae@med.id.yamagata-u.ac.jp
小櫃 由樹生	国際医療福祉大学 三田病院 血管外科	教　授	obitsu521@gmail.com
高野 邦夫	山梨大学医学部附属病院 第二外科（小児外科）	講　師	kunio@cj8.so-net.ne.jp
江口　豊	滋賀医科大学医学部附属病院　救急・集中治療部	教　授	eguchi@belle.shiga-med.ac.jp
湯川 真生	近畿大学医学部奈良病院 乳腺外科・消化器外科	准教授	yukawa@nara.med.kindai.ac.jp
池田 正孝	大阪大学大学院 医学系研究科 消化器外科	助　教	mikeda@gesurg.med.osaka-u.ac.jp
左近 賢人	西宮市立中央病院（外科）	院　長	sakon@nishi.or.jp
小代 正隆	鹿児島県立大島病院（血液・血管外科）	院　長	masa-ojiro@po.minc.ne.jp
玉井 佳子	弘前大学医学部附属病院 輸血部	講　師	ytamai@cc.hirosaki-u.ac.jp
伊藤 俊広	仙台医療センター 血液内科	医　長	toshi_ito_ito@yahoo.co.jp
杉田 憲一	獨協医科大学 小児科学	教　授	genpakus1012@nifty.com
内海 英貴	群馬大学医学部 生体統御内科	助　教	huchiumi@gunma-u.ac.jp
瀧　正志	聖マリアンナ医科大学 横浜市西部病院 小児科	教　授	m2taki@marianna-u.ac.jp
朝倉 英策	金沢大学附属病院 高密度無菌治療部	准教授	hasakura@med3.m.kanazawa-u.ac.jp
松下　正	名古屋大学医学部附属病院 輸血部	教　授	tmatsu@med.nagoya-u.ac.jp
柏木 浩和	大阪大学大学院医学系研究科 血液・腫瘍内科	助　教	kashi@hp-blood.med.osaka-u.ac.jp
日笠　聡	兵庫医科大学 内科学講座 血液内科	講　師	parasol@mua.biglobe.ne.jp
羽藤 高明	愛媛大学医学部附属病院 輸血・細胞治療部	病院教授	takahato@m.ehime-u.ac.jp
西川 拓朗	九州がんセンター 小児科		adu44150@ams.odn.ne.jp

後天性血友病 XIII(13)[出血性後天性第 XIII(13)因子欠乏症] 調査票*1 （初回）

2011.06.12

施設・診療科名			調査票記載医師名と記入年月日	医師名	記入年月日 2011 年 月 日
患者略名(匿名化)*2		登録番号*2	発症(出血)の年月日	西暦 年 月 日	
患者生年月(年齢)・性別	西暦 年 月生(才) 男・女		出血の有無(過去)初発時・最悪時	出血の頻度(初発時・最悪時)：	出血部位(初発時・最悪時)：
原(基礎)疾患名	有 ( ) 不明		出血の有無(現在)	出血の頻度：	出血部位：
F13 低下に関する手術・輸血歴・薬剤歴等			貧血の有無(Hb 値)	有・無	Hb 値 (g/dL)
現在の状況	入院・外来 (西暦 年 月現在)		創傷治癒異常の有無	有 (具体的に) 無	
診断の年月日	西暦 年 月 日		出血初発時の第 13 因子(F13 投与前・後)	第13 因子活性(F13:C)： %	第13 因子抗原量(F13:Ag)： %
診断／転帰	病名( )/ 不変・軽快 死亡(死因)		最悪時の第 13 因子(F13 投与前・後)	第13 因子活性(F13:C)： %	第13 因子抗原量(F13:Ag)： %
止血の年月日	西暦 年 月 日		止血時の第 13 因子(F13 投与前・後)	第13 因子活性(F13:C)： %	第13 因子抗原量(F13:Ag)： %
止血時の第13 因子製剤	名称( ) 量 (単位) 体重(kg)		家族*5 の第 13 因子(続柄： と)	第13 因子活性(F13:C)： %と %	第13 因子抗原量(F13:Ag)： %と %
出血治療・予防の方法	F13 以外の血液製剤( )・抗線溶薬( )・その他( )				
インヒビターの有無*3	現在有・無・不明・過去に有		インヒビター確認年月日	西暦 年 月 日／不明	
インヒビターの治療方法	免疫抑制薬： ステロイド ( ) リツキシマブ ( ) その他 ( )			血漿交換：	その他：
	治療効果：薬剤名( )により インヒビターが(消失・減少・不変・上昇)した				
直近のフィブリノゲン(Fbg)濃度	Fbg ( ) mg/dL	その他*4			

*1 調査票の Word ファイルをメールでお送りしますので、ご記入の上、事務局(山形大学)まで返送してください。メールが使えない場合は郵送でも結構です。
*2 患者略名は各施設が匿名化している略名等を、登録番号は貴施設／科内での患者番号等を記載してください。
*3 なお、インヒビターの測定は事務局でも精密に行いますので、予め連絡の上検体をお送りください。2, 3 ヶ月程度の間隔で 2 回以上実施してください。
*4 HIV, HCV, HBV など陽性の場合は、各施設の取り決めに従って検体にその旨記載してください。
*5 家族は、なるべく多数の症例本人の両親、子供等の血縁関係者としてください。
記入上の不明な点については、後天性血友病 XIII(13)研究班 事務局（山形大学医学部 分子病態学 Tel：023-628-5276）にお問い合わせください。
下線部は、適当な項目に○を付けてください。

後天性血友病 XIII(13)[出血性後天性第 XIII(13)因子欠乏症]　臨床経過表

2010.11.05

病名		患者略名*		年齢		性別	

*調査票と一致させてください。

						備考
治療	F13 製剤					
	輸血など					
	免疫抑制薬					
	その他					
症状	① 出血					
	②創傷治癒					
	③その他					
検査値	F13 活性(%)					Hb 値 (g/dL)
	100					
	80					16
	60					12
	40					8
	20					4
	0					0
	抗 F13 抗体					
その他	(血小板数)					
	(PT)					
	(APTT)					
	(FDP など)					
年月日		年月日 (10/9/XX) 第一病日				

後天性血友病 XIII(13)※についてのアンケート

2011.11.09

（※ 出血性後天性第 XIII(13)因子欠乏症の一部）

施設名（　　）診療科名（　　）記入者名（　　）通算番号(　　)

メールアドレスあるいは連絡先（　　）

① ここ 1 年間に、貴科で、PT、aPTT が正常(基準)範囲あるいは正常(基準)範囲に近いのに拘らず「原因不明の」出血症状を呈する症例(死亡例も含む)を診療されたことがありますか？

ある　・　ない　（いずれかに○をつけてください。）

①で「ある」と回答された方のみ、②と③へお進みください。

② もし、出血時間を測定されていたらご記入ください。

測定年月日 20　　年　　月　　日　　出血時間(　　分　　秒)　測定方法(　　)

③ 症例の凝固第 13 因子(F13)活性（あるいは抗原量）を測定されましたか？

測定した　・　測定しなかった　（いずれかに○をつけてください。）

③で F13 活性／抗原量を「測定した」と回答された方のみ、④～⑨へお進みください。
（空欄があっても結構です。複数の症例を経験された方は、本用紙をコピーしてご記入ください。）

④ 以下について、お知らせください。

性別（ 男・女 ）年齢（　　才）基礎疾患（ 有 ；疾患名　　・ 無 ）

⑤ 症例の F13 値をご記入ください。(F13 投与　前・後のいずれかに○をつけてください。)

a. 出血初発時の第 13 因子（F13 投与　前 ・ 後 ）測定年月日（20　年　月　日）活性値（　%）抗原量（　%）
b. 止血時の第 13 因子(F13 投与　前 ・ 後 ）測定年月日（20　年　月　日）活性値（　%）抗原量（　%）
c. 現在／直近の第 13 因子（F13 投与　前 ・ 後 ）測定年月日（20　年　月　日）活性値（　%）抗原量（　%）

⑥ もし、以下の項目を測定されていたらご記入ください。

	測定年月日					
a.	20	年	月	日	F13-B 抗原量（　%）	F13 インヒビター（ 有 ・ 無 ）
b.	20	年	月	日	Fibrinogen 量（　mg/dL）	測定方法（　）
c.	20	年	月	日	α_2PI 活性（　%）	α_2PI 抗原量（　）
d.	20	年	月	日	FDP（　μg/mL）	
e.	20	年	月	日	D-dimer（　μg/mL）	
f.	20	年	月	日	PIC*（　μg/mL）	*プラスミン-α_2プラスミンインヒビター複合体
g.	20	年	月	日	血小板凝集能（　%）	惹起物質名と濃度（　；　）
					血小板凝集能（　%）	惹起物質名と濃度（　；　）

⑦ その症例の出血症状について、該当するものに○をつけてください。

出血部位(1)（ a.筋肉内、 b.皮下、 c.胸腔、 d.腹腔、 e.頭蓋内、f.その他；　）
出血部位(2)（ a.下肢、 b.体幹、 c.上肢、 d.頭部、 e.その他；　）
出血の誘因（ a.外傷；　、 b.手術；　、 c.薬剤；　、
d.妊娠／分娩；　、 e.その他；　）
その他：後出血、ウージング様出血などの出血の性状・特徴、創傷治癒の異常（遅延、異常肉芽等）など
（　）

⑧ その症例の出血に対する治療について、該当するものに○をつけてください。

薬剤［ a.F13 製剤(名前　）、b.免疫抑制薬(名前　）、
c.抗線溶薬(名前　）、d.その他；　］
薬剤の使用期間（ a.３ヶ月、 b.６ヶ月、 c.１年間、 d.その他；　）
処置（ a.血漿交換、 b.その他；　）
処置の期間（ a.３ヶ月、 b.６ヶ月、 c.１年間、 d.その他；　）
効果・予後（ a.止血が得られた、 b.F13 が正常化した、 c.治療中、 d.その他；　）

⑨ その症例の治療上、問題になった事柄がありましたら、自由にご記入ください。

ご協力ありがとうございました。
［12 月 15 日(木)までにお送りください。］

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後天性血友病 XIII(13)研究班長　一瀬　白帝

主治医に対するメールアンケート①
2011.12.19 実施

(1) 出血する F13 活性レベル（　　）%

(2) 止血する F13 活性レベル（　　）%

(3) トランサミン（あるいはアプロチニン）が止血に効果があったか　（　有・無　）

(4) 他の有効な止血治療があったか（　有・無　）

（ある場合、具体的に；＿＿＿＿＿＿＿＿＿＿＿＿＿＿）

(5) その他

（検査、診断、治療についての御考え、疑問等を具体的に；＿＿＿＿＿＿＿＿）

主治医に対するメールアンケート②
2011.12.27 実施

(1) 本疾患の止血治療における F13 濃縮製剤投与の量と期間

（＿＿＿＿＿）出血の場合、（＿＿＿＿＿）単位／日

あるいは　（＿＿＿＿＿）単位／kg／日　期間（＿＿＿＿＿）日

（＿＿＿＿＿）出血の場合、（＿＿＿＿＿）単位／日

あるいは　（＿＿＿＿＿）単位／kg／日　期間（＿＿＿＿＿）日

(2) 本疾患の止血治療における抗線溶薬投与量と期間

（＿＿＿＿＿）出血の場合、（トランサミン；＿＿＿＿＿）mg／日

あるいは　（＿＿＿＿＿）mg／kg／日　期間（＿＿＿＿＿）日

（＿＿＿＿＿）出血の場合、（その他(具体的に)＿＿＿＿＿；＿＿＿＿＿）mg／日

あるいは　（＿＿＿＿＿）mg／kg／日　期間（＿＿＿＿＿）日

(3) 抗 F13 自己抗体に対する免疫抑制薬の投与量と期間

（プレドニンゾロン）の場合、（＿＿＿＿＿）mg／日

あるいは　（＿＿＿＿＿）mg／kg／日　期間（＿＿＿＿＿）日

（エンドキサン）の場合、（＿＿＿＿＿）mg／日

あるいは　（＿＿＿＿＿）mg／kg／日　期間（＿＿＿＿＿）日

（リツキサン）の場合、（＿＿＿＿＿）mg／m2／回

あるいは　（＿＿＿＿＿）mg／m2／回（＿＿＿＿＿）回

その他（具体的に；＿＿＿＿＿）の場合、（＿＿＿＿＿）mg／日

あるいは　（＿＿＿＿＿）mg／kg／日　期間（＿＿＿＿＿）日

主治医に対するメールアンケート③
2012.01.16 実施

４月１日より（実際は３月から）本疾患診断のための検査は、

(1) 凝固第 XIII(13)因子活性測定（交叉混合試験）：通常価格（基本単価）4500 円×３（本人、健常者、１：１混合血漿）

(2) アルファ 2PI 活性測定：通常価格（基本単価）2500 円×４（本人、健常者の血漿と血清）

(3) 凝固第 XIII(13)因子抗原量測定：通常価格（基本単価）4500 円×１（本人）

の全額負担となるものと思われます。価格は SRL と貴院との直接交渉となり、班研究の割引価格は適用されません。

F13 インヒビター検出のスクリーニングには、項目(1)は不可欠ですが、経理処理が自己負担になる場合、検査の実施が可能か否か、費用を誰が負担するのか率直に御記入ください。

（　実施する　・　実施しない；具体的なコメント＿＿＿＿＿＿＿＿＿＿）

（　検査費用を誰が負担するのか；＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿）

また、インヒビターの可能性がある場合、山形大学（あるいは他の施設）で精査する必要がありますが、検体を冷凍で送付することが可能か否か、費用を誰が負担するのか率直に御記入ください（送料は発送者払い。配送費用は 1000～2000 円と予想される。）

（　可能　・　不可能；具体的なコメント＿＿＿＿＿＿＿＿＿＿）

（　検査費用を誰が負担するのか；＿＿＿＿＿＿＿＿＿＿＿＿）