bjh short report

# Congenital factor XIII deficiency: comprehensive overview of the FranceCoag cohort

**Séverine Bouttefroy,[1] Sandrine Meunier,[1] Vanessa Milien,[2] Mohamed Boucekine,[2] Pierre Chamouni,[3] Dominique Desprez,[4] Annie Harroche,[5] Audrey Hochart,[6] Marie Françoise Thiercelin-Legrand,[7] Bénédicte Wibaut,[6] Hervé Chambost,[2,8] Lucia Rugeri[1] and on the behalf of the CoDeC study group**

*[1]Hospices Civils de Lyon - Unite d'Hemostase Clinique, Hôpital Cardiologique Louis Pradel, Lyon, France, [2]AP-HM, FranceCoag, Marseille, France, [3]Hemophilia Care Center, Rouen University Hospital, Rouen, France, [4]Haemophilia Treatment Centre, Strasbourg University Regional Hospital, Strasbourg, France, [5]Haemophilia Treatment Centre, APHP, Hospital Necker, Paris, France, [6]Haematology and Transfusion, CHU Lille, Hospital Necker, Lille, France, [7]Haemophilia Treatment Centre, University Hospital of Toulouse, Toulouse, France and [8]Hemophilia Care Center, La Timone Hospital and Aix Marseille Univ, INSERM, INRA, C2VN, Marseille, France*

Received 13 April 2019; accepted for publication 13 June 2019

Correspondence: Séverine Bouttefroy, MD, Unite d'Hemostase Clinique, Hopital Cardiologique Louis Pradel, 28, avenue Doyen J. Lepine, F-69500 Bron, France.
E-mail: severine.bouttefroy@gmail.com

## Summary

This FranceCoag network study assessed 33 patients with congenital factor XIII (FXIII) deficiency presenting FXIII levels <10 iu/dl. Diagnosis was based on abnormal bleeding in 29 patients, a positive family history in 2, recurrent miscarriages in 1 and was fortuitous in 1. Eighteen patients (62·1%) presented life-threatening umbilical or intracranial haemorrhages (ICH). Seven of the 15 patients who experienced ICH were diagnosed but untreated, including 3 with secondary neurological sequelae. All pregnancies without prophylaxis (26/26) led to miscarriages *versus* 3/16 with prophylaxis. In patients exhibiting FXIII levels <10 iu/dl, prophylaxis could be discussed at diagnosis and at pregnancy. Further controlled prospective studies are needed.

**Keywords:** factor XIII, rare bleeding disorder, registry, epidemiology, prophylaxis.

Congenital Factor XIII (FXIII) deficiency is a rare bleeding disorder (RBD) that affects the final stage of the coagulation process. One in every 2 million live births is affected, with a higher prevalence in consanguineous families (Hsieh & Nugent, 2008; Muszbek *et al*, 2011; Odame *et al*, 2014). The minimum FXIII activity level required to prevent major bleeding remains controversial in the absence of controlled prospective data (Menegatti *et al* 2017; Dorgalaleh *et al*, 2017; Mumford *et al*, 2014). Signs of FXIII deficiency range from life-threatening bleeding, such as umbilical cord bleeding (UCB; 80% of cases) or intracranial haemorrhages (ICH; 30% of cases), to milder forms, like skin bleeding (Hsieh & Nugent, 2008). Recurrent miscarriages are common in women with a severe FXIII deficiency (Odame *et al*, 2014). Diagnosis is challenging because standard coagulation tests remain normal and the specific FXIII assays required for diagnosis lack accuracy for low FXIII levels. Only heterogeneous case studies have addressed FXIII deficiency, yet none have involved a French cohort.


doi: 10.1111/bjh.16133

We herein present a comprehensive overview of patients with congenital FXIII deficiency (FXIII levels <10 iu/dl) at diagnosis who were followed in France.

## Methods and materials

This retrospective study, conducted from October 2017 to July 2018, was based on the FranceCoag Network (Doncarli *et al*, 2019), a national prospective cohort of patients with inherited coagulation factor deficiencies. The patients, followed-up in a haemophilia centre, presented FXIII activity levels <10 iu/dl. The data collected included: demographics; personal and family bleeding histories; circumstances of diagnosis; clinical presentations; laboratory coagulation tests; type of treatment regimen; pregnancies and inhibitor development.

The data were anonymously retrieved from the FranceCoag database using a specially-designed case record form. Due to the study's retrospective design and anonymised data collection, neither ethics committee approval nor written patient consent was required. The data were expressed as mean ± standard deviation, median ± interquartile ranges or percentages, with comparisons made using the Mann-Whitney test. Statistical significance was set at <0·05.

## Results

Between October 2017 and July 2018, 33 patients (54·5% male) from 31 families were included, comprising 20 Caucasians, 12 North Africans and 1 South American. Parental consanguinity was reported in 50% (16/32). Four patients

**Table I.** Characteristics of patients.

| Patient | Gender | Age at diagnosis (years) | Familial history of coagulopathy | First clinical presentation | FXIII activity (iu/dl) | Delay to initiation of LTP (years) | Treatment regimen | Bleedings after diagnosis and before initiation of prophylaxis |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 1·48 | N | ICH | 1 | 29·4 | ODT then LTP | Yes (psoas bleeding) |
| 2 | M | 0 | N | UCB | 4 | 3·5 | LTP | No |
| 3 | M | 0·03 | N | UCB | 1 | 0·4 | LTP | No |
| 4 | F | 3·06 | N | Prolonged bleed | 1 | 16·7 | LTP | Yes (ICH) |
| 5 | F | 0·08 | N | UCB | 1 | 7·5 | ODT then LTP | No |
| 6 | F | 12·07 | N | None | 1 | 14·5 | LTP | No |
| 7 | F | 15·16 | N | UCB, Gynaecological bleed | 9 | 1·5 | LTP | No |
| 8 | F | 1·63 | N | ICH | 5 | 0 | LTP | No |
| 9 | F | 0·03 | N | UCB | 1 | 0 | LTP | No |
| 10 | F | 31·23 | N | Miscarriage | 1 | 0 | LTP | No |
| 11 | F | 0·03 | N | UCB | 1 | 11 | LTP | Yes (ICH) |
| 12 | M | 0 | Y | Family History | 1 | 2·5 | LTP | Yes (ICH) |
| 13 | F | 0·04 | N | UCB | 1 | 0 | LTP | No |
| 14 | M | 3·84 | N | ICH, UCB | 4 | 41 | LTP | Yes (ICH) |
| 15 | M | 1·84 | N | Haematoma | 2 | 0 | LTP | No |
| 16 | M | 0 | Y | ICH | 3 | 0 | LTP | No |
| 17 | M | 4·43 | N | UCB | 1 | 21·2 | ODT then LTP | No |
| 18 | F | 0·26 | N | UCB, ICH | 7 | 3·4 | LTP | No |
| 19 | M | 1·53 | N | UCB, ICH | 6 | 17·4 | LTP | Yes (ICH) |
| 20 | F | 35·01 | N | UCB | 6 | NA | LTP | No |
| 21 | M | 0·07 | N | ICH | 3 | 0 | LTP | No |
| 22 | F | 26·61 | Y | Prolonged Bleed | 1 | 0 | LTP | No |
| 23 | M | 0·03 | N | UCB | 6 | 1 | ODT then LTP | Yes (ICH) |
| 24 | M | 0 | Y | Family history | 5 | 0 | LTP | No |
| 25 | F | 1·68 | N | UCB | 1 | 0 | LTP | No |
| 26 | M | 0·04 | N | UCB | 9 | 0 | LTP | No |
| 27 | F | 1·76 | N | ICH | 9 | 0·8 | LTP | No |
| 28 | M | 0·90 | N | Prolonged bleed | 1 | 29·3 | ODT then LTP | No |
| 29 | M | 0·09 | N | UCB | 4 | 1 | LTP | Yes (UCB and ICH) |
| 30 | M | 0·98 | N | ICH | 9 | 0 | LTP | No |
| 31 | M | 0·03 | N | UCB | 1 | 0 | LTP | No |
| 32 | M | 0·03 | N | UCB | 1 | 0 | LTP | No |
| 33 | M | 0·06 | N | UCB | 1 | 0 | LTP | No |

F, female; ICH, intracranial haemorrhage; LTP, long term prophylaxis; M, male; N, no; NA, not available; ODT, on demand treatment; UCB, umbilical cord bleeding; Y, yes.

**Table II.** Circumstances for diagnosis of congenital FXIII deficiency.

| | N (%) | Life threating manifestation, N (%) |
|---|---|---|
| Haemorrhagic manifestations | 29 (87·9) | 18 (54·5) |
| Umbilical cord bleeding | 19 (57·6) | 9 (27·3) |
| Intracranial bleeding | 9 (27·3) | 10 (30) |
| Prolonged bleeding | 6 (18·2) | |
| Ecchymosis/haematoma | 5 (15·2) | |
| Cephalhaematoma | 2 (6) | |
| Gum bleeding | 2 (6) | |
| Haemarthrosis | 1 (3) | |
| Menometrorrhagia | 1 (3) | |
| Bleeding during surgery | 1 (3) | |
| Family history | 2 (6) | |
| Non-haemorrhagic manifestations | 2 (6) | |
| Spontaneous abortion | 1 (3) | |
| Incidental diagnosis | 1 (3) | |

(12·1%) presented a family history of coagulation disorders, though FXIII deficiency was well-established in a sibling in only two.

The population's median age was 24·8 (18·7–38·1) years, and the median follow-up duration was 21·9 (17·1–31·4) years. The median age at diagnosis was 3·2 (0·39–21·71) months: 0·56 (0·32–11·29) for men and 19·81 (2·02–160·76) for women. This difference was due to several women having been diagnosed following recurrent miscarriages or metrorrhagia, without prior bleeds. No difference was observed concerning the patients' FXIII activity levels at diagnosis (3·44 iu/dl for males, 3·07 iu/dl for females). For those diagnosed post-bleeding ($n$ = 29), the median age at diagnosis was 3·2 (0·39–21·61) months *versus* 21·7 (12·1–31·29) years for those diagnosed in the course of non-bleeding events ($P$ = 0·044). The patients' characteristics and first clinical presentations are summarized in Table I. Overall, 29 patients (87·9%) were diagnosed following abnormal bleeding, including 65·5% UCB and 31·0% ICH. Initial haemorrhages were life-threatening in 18 (62·1%) patients, namely 9 ICH, 8 UCB and 1 ICH + UCB. Diagnosis was based on positive family histories in two patients, miscarriages in one, and was fortuitous in one (Table II).

### *Factor XIII levels and standard coagulation tests*

Predictably, 21 patients (63·6%) with available prothrombin time (PT) and activated partial thromboplastin time (APTT) tests displayed normal values. The median FXIII activity level at diagnosis was 1 iu/dl (range: 1–5·2) (Table I). Genetic defects were identified in 23 patients (72·7%) with FXIII deficiency due to A-subunit abnormalities: homozygous for 70·6%, and double heterozygous for 23·5%. No mutation was identified for one patient, and nine patients had no genetic testing.

### *Implemented treatments and bleeding complications*

All patients had received or were receiving treatment (FXIII concentrate): 75·8% long-term prophylaxis (LTP) and 24·2% on-demand treatment, alternating with LTP. LTP was initiated at diagnosis in 15 patients (45·5%) and as a second step in 17 (51·5%, missing data for 1), with a delay of 3·4 *versus* 11 years in bleeding *versus* non-bleeding patients. No difference was noted between clinical manifestation at diagnosis in patients who received prophylaxis at diagnosis and the others.

During the 22-year follow-up, serious bleeding occurred in 22 patients (66·7%): ICH in 12 (54·5%), UCB in 7 (31·8%), and combined intracranial and other bleeding types (psoas bleeding or UCB) in 3 (13·6%). After diagnosis, no bleeding was observed after the start of prophylaxis treatment. Overall, 15 patients experienced ICH: 8 were undiagnosed, and 7 were diagnosed but untreated. Neurological complications, such as seizures, neurological deficits and cognitive dysfunction, were described in 8 patients with ICH, three of whom were diagnosed but untreated. One patient developed a FXIII inhibitor three months after initiating therapy, which was eradicated after five years with intensified prophylactic treatment (as haemophilia immune tolerance therapy).

### *Pregnancies*

Of the 12 women (66·7%) with childbearing potential, 8 became pregnant, resulting in 42 – though only 13 full-term – pregnancies. All pregnancies in women without prophylaxis (26/26) were associated with miscarriages *versus* 3/16 (18·8%) in those receiving prophylaxis ($P$ < 0·001). Complications occurred in two women with live births: one pulmonary embolism at Week 6 post-delivery (not related to FXIII substitution), and one new-born death at Week 1 due to prematurity.

## Discussion

Our cohort involved the entire set of French patients with FXIII deficiency <10 iu/dl registered in the FranceCoag Network (Doncarli *et al*, 2019)), which relies on comprehensive data concerning haemophilia and RDBs from 40 centres. Our study is one of the largest and most homogeneous FXIII deficiency cases studied to date regarding disease definition, severity and families included ($n$ = 31). Though the research data were well-verified and monitored by the FranceCoag Network, certain data not available in this registry could be a limitation of our study. This retrospective characteristic of our study is responsible for information bias, and because FXIII congenital deficiency is rare, we observed a lack of statistical power.

While the definition of the severity of FXIII was well-established in the patients studied, the threshold of 10 iu/dl, which was chosen because it is the inclusion criteria in the

national registry, can be discussed: the minimum FXIII activity level required to prevent major bleeding remains controversial in the literature. Various cut-offs have been proposed: 4 iu/dl by Dorgalaleh and Rashidpanah (2016), 10 iu/dl by the United Kingdom Haemophilia Centre Doctors' Organization (if personal of familial bleeding history exists) (Mumford *et al*, 2014) 15 iu/dl by the Prospective RBD Database (Menegatti *et al* 2017). As such, prospective controlled studies are needed to define the best threshold to prevent major bleedings.

In our study, only 45·5% of patients underwent LTP despite severe and/or early-onset bleeding, such as UCB (57·6%) and ICH (27%). ICH arose in 15 patients (45·5%), 7 of whom were diagnosed for congenital FXIII deficiency but untreated (and 3/7 had neurological sequelae).

As no major bleeding was observed once prophylaxis was initiated, we suggest, as reported by some authors regarding the life-threating risk and complications in patients with FXIII <10 iu/dl and/or severe clinical phenotypes at diagnosis, that prophylaxis could be discussed.

All pregnancies in women without prophylaxis (26/26) resulted in miscarriages *versus* 3/16 (18·8%) in those receiving prophylaxis. Our results suggest that prophylactic administration of FXIII concentrates throughout pregnancy could be discussed to prevent miscarriage. While the required minimal FXIII level is still uncertain, Menegatti and Peyvandi (2019) recommended maintaining FXIII levels >30 iu/dl, and Dorgalaleh and Rashidpanah (2016)recommended a threshold of FXIII activity >12 iu/dl throughout pregnancy and >35 iu/dl during delivery. Our results show that prophylaxis could prevent miscarriage, even if this study could not determine a cut-off for minimum-required FXIII activity (FXIII levels during pregnancy were not available in the registry).

Rare bleeding disorders are very rare and heterogeneous, with variable associations between coagulation factor activity and bleeding. Our results confirm the helpfulness of prophylaxis in FXIII deficiency with severe clinical features. As the widely used assay for the measurement of FXIII activity lacks accuracy for low FXIII levels of <10 iu/dl, the assays are unable to define minimum residual levels, which affects both diagnosis and therapeutic management. Further studies are needed to determine a threshold of the minimum FXIII activity needed under prophylaxis to avoid major bleeding and miscarriage.

## Conflicts of interest

All authors declared no conflicts of interest.

## Acknowledgements

S. Bouttefroy performed the research, designed the research study analysed the data and wrote the paper. S. Meunier, H. Chambost and L. Rugeri performed the research designed the research study, contributed to the acquisition of data and wrote the paper. V. Milien designed the research study, performed the research, analyzed the data and reviewed the paper; M. Boucekine analysed the data and reviewed the paper; P. Chamouni, D. Desprez, A. Harroche, A. Hochart, MF. Thiercelin-Legrand & B. Wibaut contributed to the acquisition of data and revised critically the paper G. Cremer wrote the paper, paid by HRFL (Hémostase Recherche Formation Lyon). We thank Hémostase Recherche Formation Lyon for medical writing of this paper. The collaboration of the CoDeC Study Group members was greatly appreciated: Karine Baumstarck, Claire Berger, Christine Biron, Mirela Chirila, Stéphane Girault, Jenny Goudemand, Benoit Guillet, Cécile Lavenu Bombled, Valérie Li Thiao Te, Maelle Mauguen, Fabrice Monpoux, Philippe Nguyen, Caroline Oudot Challard, Brigitte Pan Petesch, and Marc Trossaert.

## References

Doncarli, A., Demiguel, V., Guseva Canu, I., Goulet, V., Bayart, S., Calvez, T., Castet, S., Dalibard, V., Demay, Y., Frotscher, B., Goudemand, J., Lambert, T., Milien, V., Oudot, C., Sannié, T., Chambost, H. & FranceCoag Network (2019) FranceCoag: a 22-year prospective follow-up of the national French cohort of patients with inherited bleeding disorders. *European Journal of Epidemiology*, **34**, 521–532.

Dorgalaleh, A. & Rashidpanah, J. (2016) Blood coagulation factor XIII and factor XIII deficiency. *Blood Reviews*, **30**, 461–475.

Dorgalaleh, A., Tabibian, S.H., Safa, M., Shams, M. & Naderi, M. (2017) Minimal factor XIII activity level to prevent major spontaneous bleeds: comment. *Journal of Thrombosis and Haemostasis*, **15**, 2279–2280.

Hsieh, L. & Nugent, D. (2008) Factor XIII deficiency. *Haemophilia*, **14**, 1190–1200.

Menegatti, M. & Peyvandi, F. (2019) Treatment of rare factor deficiencies other than hemophilia. *Blood*, **133**, 415–424.

Menegatti, M., Palla, R., Boscarino, M., Bucciarelli, P., Muszbek, L., Katona, E., Makris, M., Peyvandi, F. & PRO-RBDD Study Group. (2017) Minimal factor XIII activity level to prevent major spontaneous bleeds. *Journal of Thrombosis and Haemostasis*, **15**, 1728–1736.

Mumford, A.D., Ackroyd, S., Alikhan, R., Bowles, L., Chowdary, P., Grainger, J., Mainwaring, J., Mathias, M. & O'Connell, N. (2014) Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *British Journal of Haematology*, **167**, 304–326.

Muszbek, L., Bagoly, Z., Cairo, A. & Peyvandi, F. (2011) Novel aspects of factor XIII deficiency. *Current Opinion in Hematology*, **18**, 366–372.

Odame, J.E., Chan, A.K., Wu, J.K. & Breakey, V.R. (2014) Factor XIII deficiency management: a review of the literature. *Blood Coagulation & Fibrinolysis*, **25**, 199–205.