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Recurrent Post Tonsillectomy Secondary Hemorrhage in Patients with Factor XIII Deficiency: A Case Series and Review of Literature

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Case series

Patients: Male, 20 • Male, 4 • Male, 27 • Male, 25 • Female, 5 • Female, 26
Final Diagnosis: Post tonsillectomy secondary hemorrhage
Symptoms: Bleeding • bleeding per oral
Medication: —
Clinical Procedure: Control of post tonsillectomy secondary hemorrhage
Specialty: Otolaryngology

Objective: Rare disease
Background: Post-tonsillectomy hemorrhage (PTH) has been reported in the literature as a serious complication after tonsillectomy that has high morbidity and can be life threatening. In cases of recurrent secondary PTH, one should consider coagulopathies as the hidden pathology. Factor XIII deficiency is very rare, suggested to be present 1 in 2 million people. Patients with undiagnosed factor XIII deficiency with secondary PTH are extremely rare.
Case Report: We report on the cases of six patients (four adults and two children) who presented with recurrent attacks of secondary PTH.
Conclusion: Recurrent, severe PTH could be related to undiagnosed hematological disorders.

MeSH Keywords: Factor XIII Deficiency • Hemorrhage • Tonsillectomy

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/900391>

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Background

Post-tonsillectomy hemorrhage (PTH) has been reported to be a serious complication after tonsillectomy that has high morbidity and can be life threatening. The incidence has been reported to range from 2% to 4% [1,2]. Primary PTH (occurrence within the first 24 hours) is generally due to inadequate hemostasis during surgery, while secondary PTH (occurrence after 24 hours) is mainly due to sloughing and infection at the site of the operation. The incidence rate varies between adults and children; a literature review suggested a PTH incidence rate of 3% in children and 10.8% in adults. Approximately 1,000 tonsillectomies are performed annually at our center and 8.9% of these patients have presented with PTH. Even if post-tonsillectomy coagulation profiles show normal values, single factor levels in cases of recurrent PTH may reveal coagulation disorders allowing the application of effective therapy.

Factor XIII, the last enzyme activated in the coagulation cascade, is a member of the transglutaminase family. This coagulation factor plays a substantial role in the stability of the clot formation through cross-linking α and γ fibrin chains. Patients with factor XIII deficiency (congenital or acquired) present with a wide spectrum of bleeding diatheses [3]. We report six cases with factor XIII deficiency which presented with recurrent attacks of PTH that required multiple admissions and surgical hemostasis attempts. To our knowledge this is the largest case series of its kind to be reported.

Case Report

All of the six cases had operations performed between June 2010 and July 2015 as inpatients. The tonsillectomies were performed using bipolar diathermy dissection. The indications for the surgeries were recurrent tonsillitis and snoring, except for the third case which was quinsy. All of our patients had no personal or family history of bleeding tendencies and no physical examination findings were suggestive of a possible bleeding disorder. Control of PTH under general anesthesia was done using bipolar diathermy and suturing of the tonsillar beds. In all of the cases, the hematologist was involved after the second attack of PTH. All patients were evaluated by routine coagulation tests including: activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen level, platelet count, and bleeding time. Further laboratory investigations were ordered by the hematologist including: Von Willebrand factor, factor VIII, and factor IX assays, all of which revealed no abnormalities. Single coagulation factors assay revealed this rare pathology in our six patient cases.

Case 1

A 20-year-old male underwent tonsillectomy. On the same day of his surgery, the patient developed primary PTH, which required bleeding control in the operation theater. The patient was discharged after four days. On the seventh day after the procedure, the patient was readmitted through the Emergency Department with a fresh attack of bleeding from the same site. The bleeding was controlled under general anesthesia. The patient's hemoglobin level dropped significantly from 13 g/dL to 8.4 g/dL. The hematologist was consulted and the coagulation profile was ordered. The results were slightly elevated PT (prothrombin time) 14.4 (control: 12) and INR 1.3. Two units of packed red blood cells (PRBC) were transfused. Subsequently, the patient experienced another two attacks of active bleeding that required control under general anesthesia. Extensive hematological workup revealed factor XIII deficiency (48%) normal range (70% to 140%). The patient was transfused with two fresh-frozen plasma (FFP) units with no further attacks of bleeding. A follow-up of factor XIII activity could not be done because the patient was a visitor and traveled back to his home country.

Case 2

A 4-year-old male presented to the Accident and Emergency Department with episodes of recurrent secondary PTH on the tenth and nineteenth post-operative day. The first episode was managed conservatively but his second attack required control under general anesthesia. The patient's hemoglobin dropped from 11 g/dL to 9.7 g/dL. His initial coagulation profile was normal. Blood factor assay studies revealed a factor XIII deficiency (15%). The patient also received one unit of FFP and subsequently had a smooth post-operative recovery. In his follow-up, seven months later, the factor XIII percentage elevated to 56.6% but still was not within normal range.

Case 3

A 27-year-old asthmatic male had three episodes of recurrent secondary PTH on the second, sixth and eleventh post-operative day, all episodes required control under general anesthesia. Apart from mild hemodynamic instability, the patient's hemoglobin level dropped significantly from 13.6 g/dL to 8.1 g/dL. He received two units of PRBC and one unit of FFP. Despite normal PT/PTT/INR values (prothrombin time/partial thromboplastin time/international normalized ratio), the patient was found to have factor XIII deficiency (57%). In his follow-up, the factor XIII percentage elevated to 62.8%.

Case 4

A 25-year-old male underwent tonsillectomy outside our institution. He experienced three episodes of recurrent PTH on

the sixth, tenth, and seventeenth post-operative day. The patient required surgical intervention for the latter two presentations. The patient's hemoglobin level dropped from 15.8 g/dL to 12.8 g/dL. He required two units of PRBC, two units of FFB, and six units of platelets. Despite normal PT/PTT/INR values, the patient was found to have factor XIII deficiency (58%). A follow-up of factor XIII activity could not be done because the patient traveled back to his home country.

Case 5

A 5-year-old female underwent tonsillectomy. She experienced two episodes of recurrent PTH on the fifth and eighth post-operative day; the first episode was managed conservatively but the second attack required control under general anesthesia with transfusion of two units of PRBC. Blood workup, including coagulation profile, was all within normal range while her single factor study revealed factor XIII deficiency (49%). A follow-up of factor XIII activity could not be done because the patient was lost to follow-up.

Case 6

A 26-year-old female who underwent tonsillectomy presented with two episodes of recurrent PTH on the fourth and twelfth post-operative day. She required surgical hemostasis at both presentations. Her hemoglobin was 12.5 g/dL which dropped to 7.7 g/dL. Transfusion of four units of PRBC and two units of FFP were deemed necessary. Although her PT/PTT/INR were normal, her single factor study revealed factor XIII deficiency (54%). The patient was lost to follow-up.

Discussion

Tonsillectomy is one of the most commonly performed surgical procedures in otolaryngology practice [4]. Tonsillectomy in adults is not as frequently performed as in children, but it is still a common procedure. PTH has been reported in the literature as a serious complication after tonsillectomy that has high morbidity and can be life threatening. PTH has been reported to range from 2% to 4% [1,2]. The mortality rate of PTH is reported to be between 0.001% and 0.006% [5]. With respect to the gender of the patients, PTH occurs more often in males [6]. Kim et al. reported a statistically higher incidence of PTH in adults while observing that the incidence varies between adults and children; 3% of PTH occurs in children and 10.8% in adults [7]. Rates of PTH that exceed 14% stand out for monitoring, and transient rates over 20% occur less often [8]. Primary PTH (within first 24 hours) is generally due to inadequate hemostasis during the surgery, while secondary PTH (after 24 hours) is mainly due to sloughing and infection at the site of the operation [6,7]. Recurrent secondary PTH is

rare. It has been reported to range from 0.37% to 0.73% of all patients undergoing tonsillectomy and around 18.3% in PTH patients. Undiagnosed coagulopathies can be an underlying pathology of recurrent, severe PTH [9].

Factor XIII is an important coagulation factor in the coagulation pathway. It maintains hemostasis via stabilizing the fibrin clot and protecting it from fibrinolysis [10]. Factor XIII deficiency, of congenital or acquired etiology, is very rare. It is suggested to be present in one in two million people, and it is more frequent in areas where consanguineous marriages are common [11]. Surgery and trauma in factor XIII deficient patients are associated with poor wound healing and patients usually have normal PT, PTT, and thrombin time [12,13].

In our case series of six patients, four adults and two children, recurrent attacks of secondary PTH required surgical intervention and administration of blood products transfusion (Table 1). Detailed coagulation investigations after hematology consultation were done on our patients.

The laboratory diagnosis of factor XIII deficiency is most commonly made using the clot solubility test. However, the test is poorly standardized and susceptible to variations in sensitivity which is between 1% and 5% factor XIII activity. Furthermore, it will only detect severe deficiencies; and not heterozygous, mild, moderate, or acquired states, which will only be identified by more specific assays. The testing process has now been simplified with the recent introduction of Berichrom FXIII chromogenic ammonia release assay (Siemens Healthcare Diagnostics, Marburg, Germany) onto the CS-2000i coagulation analyzer (Sysmex UK Ltd., Milton Keynes, UK), which unlike most coagulation analyzers is capable of monitoring the reaction at 340 nm [14]. We performed Berichrom FXIII chromogenic ammonia release assays upon request of the hematology consultant at our institution.

Severe PTH can be life threatening due to airway obstruction and/or hypovolemic shock. For this reason, managing active bleeding is preferable rather than waiting for spontaneous resolution, otherwise major hemorrhage may follow [15].

Obtaining routine coagulation studies for preoperative assessment in tonsillectomy patients is still under debate. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) recommends performing coagulation and bleeding workup if an abnormality is suspected by personal or family history or if the family history is unavailable, or physical examination findings are suggestive of a possible bleeding disorder [16]. On the other hand, some studies showed that there is no difference in the rate of PTH in patients with abnormal coagulation values compared with patients with normal coagulation values obtained preoperatively; PT and/or PTT have poor sensitivity in detecting serious bleeding abnormality [4].

Table 1. Epidemiology data of all six patients with factor XIII deficiency.

Patient No./Sex/ Age (year)	No. of ED visits	POD, No.	Blood transfusion	Surgical Intervention	Factor XIII activity level
1/M/20	4	1, 7, 9, 13	2 PRBC's, 2FFP	Y, Y, Y, Y	48%
2/M/14	2	10, 19	1FFP	N, Y	<15%
3/M/17	3	26, 11	2 PRBC's, 1FFP	Y, Y, Y	57%
4/M/25	3	6, 10, 17	2 PRBC's, 2FFP, 6PLT	N, Y, Y	58%
5/F/5	2	5, 8	2 PRBC's	N, Y	49%
6/F/26	2	4,12	4 PRBC's	Y, Y	54%

No. – number; M – Male, F – Female, ED – Emergency Department; POD – Post-operative day; PRBC's – packed red blood cell; FFP – fresh frozen plasma; PLT – platelet; Y – yes, N – no.

Table 2. Laboratory data of all six patients with factor XIII deficiency.

Patient No.	Hemoglobin g/dl (pre-op – at presentation)	Coagulation profile at time of bleeding (PT, APTT, INR)	Factor XIII activity level	Factor XIII activity level in follow-up
1	13 – 8.4	14.4, 29.1, 1.3	48%	N/A
2	11 – 9.7	9, 28.3, 0.9	<15%	56.6%
3	13.6 – 8.1	9.8, 33, 1.4	57%	62.8%
4	15.8 – 12.8	9, 25, 1.0	58%	N/A
5	12.4 – 9.6	8.7, 23.8, 1.0	49%	N/A
6	12.5 – 7.7	10.2, 38, 1.4	54%	N/A

No. – number; PT – prothrombin time; APTT – activated partial thromboplastin time; INR – international normalized ratio; N/A – not available.

Since undiagnosed hematologic disorders may contribute to the etiology of recurrent PTH, such patients require hematological consultation with advanced coagulation investigations including fibrinogen level, platelet function, and analytical evaluation of coagulation factors [9]. Single factor levels may reveal coagulation disorders allowing the application of an effective therapy, as in our case series. Five of the six patients had PT/PTT/INR measured pre-operatively and they were within normal range. At the time of presentation, three patients had slightly elevated INR readings of 1.3, 1.4, and 1.4 (Table 2). This exceptional coagulation abnormality of factor XIII deficiency was found after a detailed workup. The presentation with severe recurrent attacks of bleeding requiring multiple entries to the operating theater for control under general anesthesia directed us to do an extensive analysis of coagulation factors which culminated in the diagnosis of factor XIII deficiency.

A review of existing literature identified two cases of recurrent PTH with factor XIII deficiency that were reported in two separate publications. One article reported a case of severe recurrent

PTH with normal coagulation profile and factor XIII level of 56% with four attacks of bleeding that all required surgical intervention with no history of prior bleeding [17]. The second article reported a case with severe recurrent PTH and factor XIII level of 57% with seven attacks of bleeding all of which required surgical intervention [18]. In our case series, all patients required surgical hemostasis using bipolar coagulation, tonsillar fossa suturing, with a range from one to four times. The range of factor XIII level was from <15% to 58% (normal range is 70% to 200%).

While managing bleeding patients with factor XIII deficiency, we also found literature where cryoprecipitate, FFP, and Fibrogammin P have been successfully administered [3,13].

Conclusions

Recurrent, severe post-tonsillectomy hemorrhage could be related to undiagnosed hematological disorders. In such patients, advanced hematological investigations can help to diagnose

such a pathology and ensure prompt treatment. Undiagnosed factor XIII deficiency presenting with recurrent secondary PTH is extremely rare.

Ethical approval

This research has already been approved by our institution's medical research and ethics committee.

Consent/assent

The patients' consent/assent was taken for the publication of this case series.

Conflict of interests

The authors of this study have no conflict of interests or financial interest, real or perceived, to disclose.

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