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Case Report

Congenital Thrombocytopenia, Intractable Menorrhagia at Menarche and Ischemic Stroke

Manal Shaker Taha[1] and Olubunmi Omolara Oniya[2]*

[1]*Department of Gynecology, Women's Hospital, Hamad Medical Corporation, Doha, Qatar*

[2]*Department of Gynecology, Sidra Medical and Research Center, Doha, Qatar*

***Corresponding Author:** Olubunmi Omolara Oniya, Department of Gynecology, Sidra Medical and Research Center, Doha, Qatar.

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Abstract

Menorrhagia is a one of the most common presenting complaints seen in modern gynecology. Common causes include those recently proposed by FIGO using the acronym PALM COEIN (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified). Very rarely menorrhagia is due to an inherited bleeding condition.

Familial congenital thrombocytopenia is also known to cause menorrhagia although case reports are very sparse and confirmed cases seldom seen in gynecology practice.

We present a rare case of severe intractable menorrhagia occurring with the first period in a 12 year old girl who has a positive family history of bleeding disorder. This patient was recently managed shortly after menarche in our unit and presented with a series of challenges in terms of diagnosis, management and therapy. There was no response to initial treatment with blood, blood products as well as antifibrinolytics. Hormonal therapy was tried eventually as bleeding continued despite these measures. The patient also suffered a thrombotic stroke with right hemiparesis while she was still bleeding. This presented a therapeutic dilemma as we had to balance measures to control the vaginal bleeding which are pro-thrombotic and at the same time trying to preventing further strokes/evolvement of her stroke with anticoagulants and thrombolytics.

Keywords: *Congenital Thrombocytopenia; Menorrhagia; Menarche; Stroke; Combined Oral Contraception Pills*

Abbreviations

Hb: Haemoglobin; RBC: Red Blood Cells; IV: Intravenous; COCP: Combined Oral Contraceptive Pills; BP: Blood Pressure; pre: Previous; BID: Twice Daily; GCS: Glasgow Coma Scale; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; MCA: Middle Cerebral Artery; PICU: Peadiatric Intensive Care Unit; GnRH: Gonadotropin-Releasing Hormone; IUCD: Intrauterine Contraceptive Device; MRA: Magnetic Resonance Angiography; DDAVP: Desmopressin; VWF: Von Willebrand factor

Introduction

The normal duration of the menstrual cycle is 1 - 7 days occurring every 21 - 35 days. What is regarded as normal amounts of blood flow is usually less than 1 pad or tampon every 3 hours.

Parameters that has been suggested to denote excessive bleeding include, clots greater than 1 inch, bleeding resulting in iron deficiency anaemia, and frequency of pad change more than every 3 hours. Whereas severe acute bleeding is defined as bleeding that requires more than 1 pad or tampon per hour or symptoms of hypovolemia [1]. Menorrhagia occurring during adolescence is usually presumed to be associated with anovulation.

Congenital thrombocytopaenia is one of the inheritable platelet disorders and is well described in literature.

Worldwide there are only 100 known cases and less than 10 in the UK [2] although the true incidence is still unknown [3]. The frequency of bleeding disorders in women diagnosed with menorrhagia at the extremes of menstruating age, ex, adolescence and perimenopause is also not known [4]. Diagnosis it still challenging as in some cases it is still misdiagnosed as acquired thrombocytopenia. There is need for careful history taking and physical examination and the use of appropriate laboratory in investigations to arrive at the correct diagnosis.

The clinical spectrum of congenital thrombocytopenias is variable ranging from severe bleeding diathesis within the first few weeks of life to milder conditions that may remain undiagnosed until adult life [5].

Clinical features may include menorrhagia which may be present from puberty, excessive bleeding following childbirth, easy bruising, excessive or prolonged nose bleeds, bleeding during dental procedures or from the gingiva and bleeding following invasive procedures [2].

Case Report

We present the case of a 12 year old girl of Middle Eastern origin. Our patient is a 12 year old girl of Middle Eastern descent who had evidence of congenital thrombocytopaenic purpura from early life. Her parents are consanguineous (1st degree cousin). She has 9 siblings but only 2 are known to suffer from congenital thrombocytopenia. This is includes an older sister who passed went through puberty, carried a pregnancy successfully and had normal labor and delivery with no bleeding.

She was delivered by elective caesarian section as her mother had had 2 previous caesarian sections. She was diagnosed at birth with familial congenital thrombocytopaenia and neutropaenia and had multiple platelets transfusions as part of her treatment.

She had multiple admissions with poor feeding and irritability and upper respiratory tract infection. In addition she had symptoms of a bleeding disorder like blood in stool, skin rash, gum bleeding and all that required platelet transfusion during the first year of life. She had been admitted around 15 times for platelet transfusion by the age of 6 years. Records show her platelets were as low as 14 x 10^3/uL at 7 months of age.

The week before menarche she was admitted with thrombocytopenia, neutropenia and fever and eventually diagnosed as having parvovirus infection. She received intravenous antibiotics, platelets transfusion and intravenous immunoglobulin as her platelet was as low as 15 x 10^3/uL. She was discharged after 5 days.

Her menarche was in October 2016 the following day after discharge. She represented to the children's emergency. At this visit her hemoglobin was 11.9 mg/dL and platelets was 18 x 10^3/uL, she was treated with Platelet transfusion and discharged home.

She was however re admitted 14 days later with ongoing heavy vaginal bleeding and had to be brought in by ambulance. She passed out in the emergency room and was noted to be passing large 7 - 9 cm clots. Her Hb had dropped from 9.1 to 7.5 mg/dL over 3 hours and her platelet was as low as 26 x 10^3/uL. She received 6 units of platelets but following a further collapse with a haemoglobin further drop to 6.6 mg/dL she was transfused with 2 units of packed RBC.

On day 2 of admission her Hb again dropped to 8.1 mg/dL and she received a further 2 units of PRBC. Gynecology consult was sought. An ultrasound of her pelvis did not show any local pathology in the uterus. Because of her ongoing severe bleeding combined oral contraceptive pill in the form of levonorgestrel 150 mcg - ethinyl estradiol 30 mg twice daily was started but despite this the following day her platelets had dropped to 58 x 10^3/uL and Hb to 7.8 mg/dL. 6 units of platelets and 2 PRBCs+ Factor IIV was transfused.

On day 5 of admission she had another attack of heavy vaginal bleeding with clots and developed hypovolemic shock. IV fluids and 2 units PRBC was given and she was started on progesterone injections 50 mg as emergency measure and COCP stopped.

By day 6 her Hb had dropped again to 7.4 mg/dL, and she received 2 units of PRBC.

On day 9 a total of 21 days since the beginning of menses she had another vasovagal attack in the bathroom. On examination her pulse was 110, BP was 87/30, she looked pale with a capillary refill of 3-4s. Her diaper was filled with large amount of blood clots. Hb was 7 mg/dL, platelets was 70 x 10^3/uL. She was resuscitated with 1500 ml saline, 600 ml fresh frozen plasma, 2 units of PRBC and 6 units of platelets. Post transfusion her hemoglobin reached 10.4 mg/dL. She also received 1 dose of Desmopressin.

On day 10 she was continued to bleed with platelets dropping to 45 x 103/uL, she received 6 units of platelets and Northesterone 10 mg BID was started.

US pelvis was repeated which showed an anteverted uterus measuring 7 by 4.2 cm. Endometrium was thickened measuring 15 mm despite prolonged bleeding and hormonal therapy.

On day 11 progesterone injection and northesterone tablets was stopped as she had not shown any response. She was then started on estradiol 2 mg tablets and received 1 dose of this.

Table 1 shows a summary of haemoglobin and platelets pre transfusion, number of platelets and packed cells transfused and haemoglobin and platelets counts post transfusion.

Day since admission	Platelets Pre Transfusion	Hb Pre Transfusion	Platelets units Transfused	Packed cells Transfused	Hb Post Transfusion	Platelets Post Transfusion
0	26	7.1 then 6.6	6 units	2 units	9.1	75
2	81	8.1	-	2 units	9	84
3	58	7.8	6 units	2 units	9.2	91
5	97	6.8	-	2 units	8.3	59
6	87	7.5	-	2 units	9.4	62
9	70	7	6units	2 units	10.4	56
10	45	9.7	6 units	2 units	11.4	93
16	60	10.4	6 units	-	9.4	90
17	51	7.8	4 units	1100 ml	14	95

Table 1: *Summary of Haemoglobin and platelets pre transfusion, number of Platelets and Packed cells transfused and Haemoglobin and Platelets counts post transfusion.*

Figure 1 shows haemoglobin and platelet count summary from October 2016 till discharge.

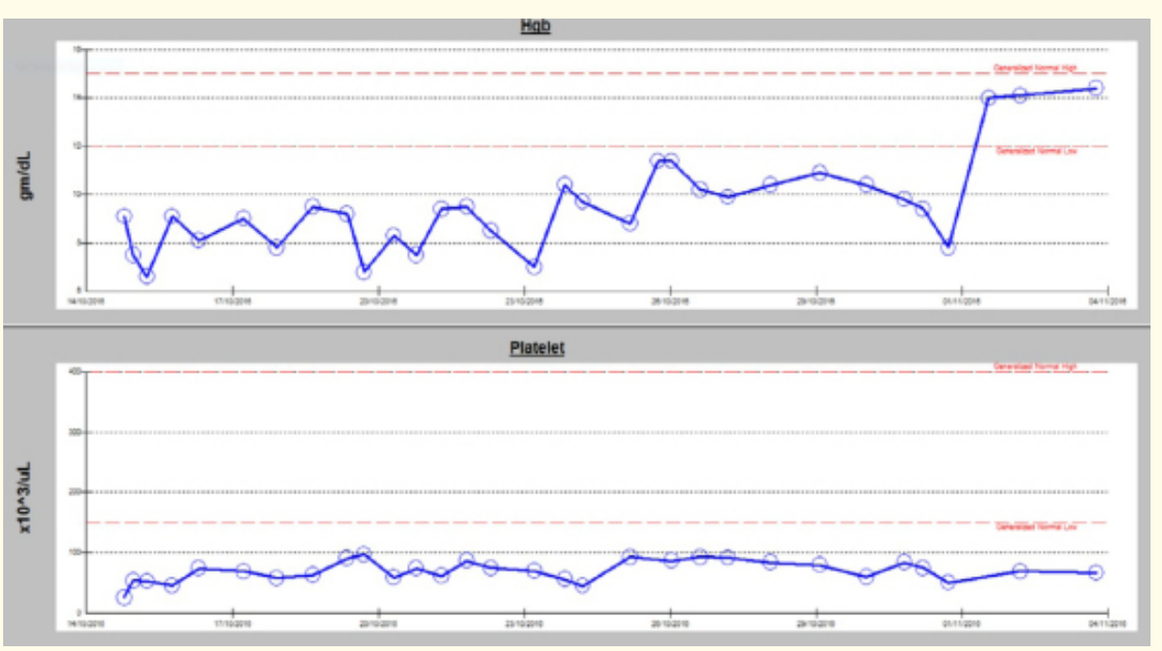

Figure 1: *Haemoglobin and Platelet count summary from October 2016 till discharge.*

Later the same day that estradiol tablets was started she developed twitching of her face for a few minutes which subsided but this was followed by weakness of her right upper and lower limb associated with slurred speech and deviation of her mouth to the left side. Vital signs were stable and cardiovascular and chest examination was unremarkable.

Neurological examination showed a GCS of 15. She was alert with spontaneous eye opening pupils were reactive, regular and equal bilaterally directly and indirectly. There was no ptosis, no nystagmus and extraocular movements were normal. There was evidence of Left upper motor neuron facial palsy, evidence of dysarthria but intact tongue movement, no evidence of uvula or palate deviation.

Power on the right upper limb was 0, Power on the right lower limb was 1, left side of the body power was 5. An urgent CT was done to rule out intracranial hemorrhage and this was normal. MRI showed left MCA ischemic stroke and the diagnosis was acute left MCA infarct, leading to right hemiparesis.

Figure 2 shows MRI pictures at the time of stroke.

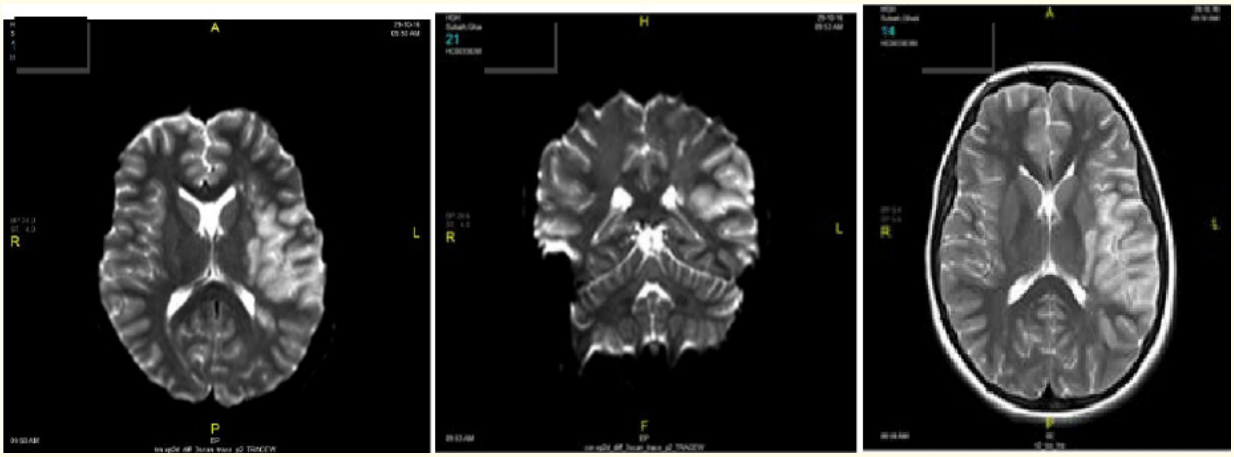

Figure 2: *MRI pictures at the time of stroke.*

Estradiol tablet was stopped and she was transferred to Peadiatric Intensive Care Unit (PICU). Because of her background history of congenital thrombocytopenia and her heavy bleeding she was not started on a thrombolytic agent. Vaginal bleeding was controlled, Hb was 11.4 mg/dL and Platelets was 83 x 10^3/uL

Unfractionated heparin was started 20 hours after onset of symptoms after explaining all risks to family. She was given Enoxaparin 0.75 mg/kg BID and Levetiracetam 10 mg/kg/dose twice daily, as she had episode of mouth twitching.

An urgent multidisciplinary team meeting consisting of the Hematologist, Pediatric intensivist, Gynecologist, and Neurologist was held.

Due to the complexity of the case with bleeding as well as ischaemic stroke in a young patient some of the measures suggested was to give GnRH agonist injections, Mirena intrauterine contraceptive device and use of Intervention radiology in case of severe life threatening bleeding, GnRH-a administration significantly decreases pituitary secretion of gonadotropins. This results in the arrest of cyclic ovarian function and a significant reduction in ovarian steroid hormone production. Therefore, the uterine endometrium is almost unexposed to any hormone influence, resulting in amenorrhea [6]. The option of Intervention radiology was for uterine vessels embolization in case of severe bleeding.

Mirena IUCD and surgical option of hysterectomy in case of life threatening bleeding was not acceptable to her family but they agreed on the use of GnRH agonist although the patient did not receive any. Keppra was continued. Echocardiogram was normal, doppler ultrasound of the carotid arteries was also normal. She was commenced on physiotherapy and occupational therapy.

On the 3rd day after her stroke, her Hb remained stable without further drop at 10.4 mg/dL and platelets of 87 x 10^3/uL. She was on anti-factor Xa 0.75 mg/kg/dose; a lower than usual dose because her anti-factor Xa was 1 IU/mL, dropped to 0.8 IU/mL then to 0.75 IU/mL, a plan to keep her hb above Hg > 10 mg/dL, platelet >70 x 10^3/uL and Anti Xa: 0.5 - 1 was made.

A repeat MRI was on the 4th day post stroke showed significant increase in the size of the left middle cerebral artery territory. Cranial MRA shows still noted loss of normal flow signal and distal runoff branches of the left MCA just distal to its bifurcation suggestive of underlying occlusion.

On day 16 (day 5 post stroke) she again had moderate amount of vaginal bleeding associated with clots, her platelets dropped to 60 x 10^3/uL. She received 6 units of platelets and was transferred from PICU to the ward. On day 17 her mother noticed increase amount of bleeding. Her HB was 7.8 mg/dL, Platelets 51 x 10^3/uL so she received 4 units of platelets and 1100 ml of PRBC.

Table 2 shows a summary of Hormonal preparations used to arrest Bleeding.

Day 2	Levonorgestrel 150 mcg + ethinyl estradiol 30 mg twice daily combined oral contraceptive (COCP)
Day 5	COCP stopped Progesterone injection 50 mg
Day 10	Northesterone 10 mg BID
Day 11	Progesterone injection stopped Northesterone tabs stopped Estradiol 2 mg 1 dose -Stroke

Table 2: *Summary of Hormonal preparations used to arrest Bleeding.*

Table 3 shows a summary of other medications used to arrest bleeding.

Day 2	Factor VII
Day 5	Factor VII (stopped on day 8)
Day 9	Desmopressin

Table 3: *Summary of other medications used to arrest bleeding.*

Her bleeding eventually settled. Currently our patient is in good general condition and is maintained on tranexamic acid 1g three times a day + iron supplements. All her neurological examination is normal with restored power and sensation. Cranial nerves are grossly normal, her motor function is within normal range as is her sensory examination.

A repeat MRI after 5 months from the stroke showed no evidence of brain parenchymal acute infarcts or haemorrhagic densities. There was evidence of left cerebral (left lentiform and white matter) or old infarcts.

She was admitted again 6 months following this episode with menorrhagia and changing up to 10 pads per day. Her platelets was 26 x 10^3/uL and HB 11.5 mg/dL. She was given platelets transfusion and her family refused Norethisterone. She was discharged home on day 4. She had a similar presentation and admission the following month and was treated with platelets transfusion.

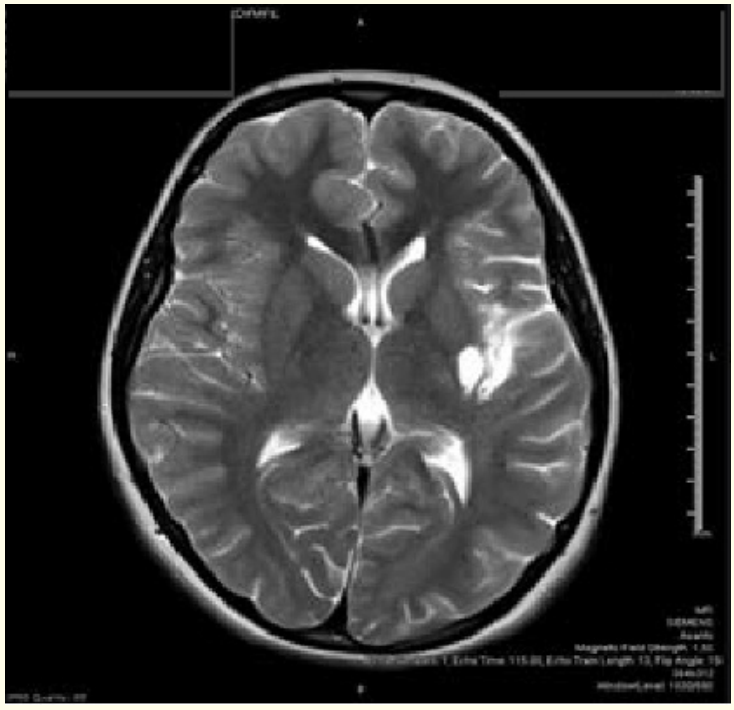

Figure 3: *Shows MRI 5 months after Ischemic Stroke.*

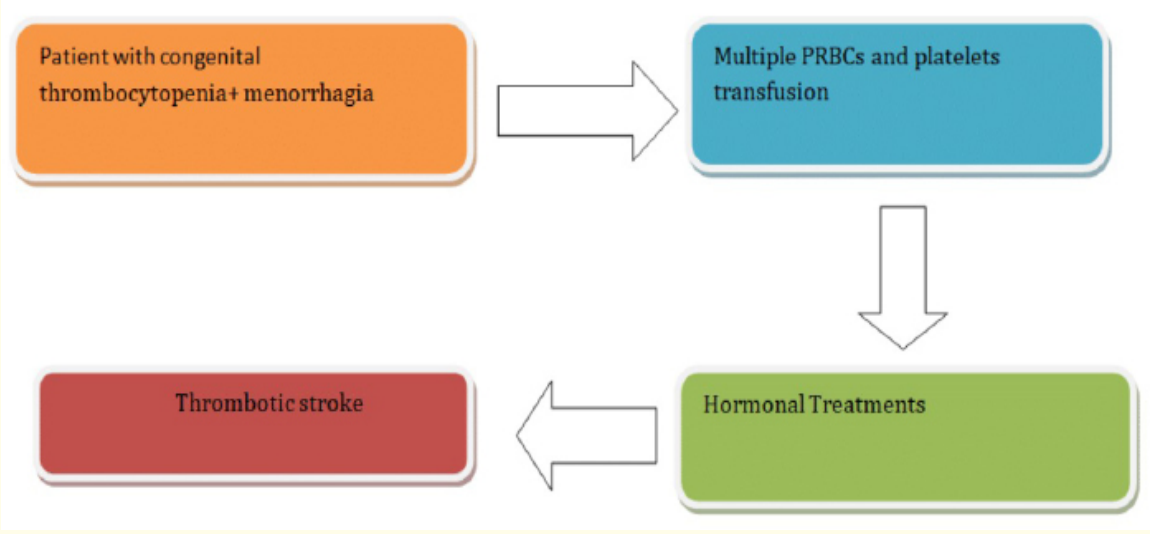

Figure 4: *Sequence of events.*

Discussion

Congenital platelets disorders are associated with a wide range of bleeding symptoms. However, there is no specific therapy for the vast majority and only severe cases need to be treated. The management of patients with congenital platelet diseases usually consists of general measures aimed at avoiding bleeding and the use of supportive therapy to control haemorrhagic episodes [5].

Although congenital thrombocytopenia is rare the first presentation may be to the Gynecologist ward with a history of menorrhagia starting at menarche. Our case was particularly a challenging because her management was complicated by the development of ischemic stroke while there was ongoing bleeding.

Medical therapy is the preferred mode of treatment for heavy menstrual cycles as it helps to avoid surgery. Many medications can be used and there is a long list of options but there is considerable variations in practice and uncertainty about the most appropriate therapy.

Desmopressin (DDAVP), a synthetic analogue of the diuretic hormone vasopressin that increases factor VIII and VWF transiently by releasing them from storage sites into the blood, is a mainstay of the therapy of patients with congenital platelet defects. Depending on the type of platelet defect, administration of DDAVP may shorten the bleeding time and its use has been suggested to be of value in some patients with congenital platelet defects, In general, the response to DDAVP varies among patients but is constant in each patient; a test dose may be of value to identify those patients who will benefit from this treatment to prevent or control future bleeds [5].

In our case despite the administration of desmopressin on day 9 she continued to bleed.

The aetiology of ischemic stroke is multifactorial. Causes may include hypovolemia with dehydration, hormonal therapy, coagulation and blood products used to control haemorrhage as well as other factors like hormonal therapy.

Hormonal therapy was tried due to ongoing severe blood loss. Studies done on progestogen-only hormonal methods as a measure to control bleeding due to menorrhagia has shown that they are generally safe and do not increase the chance of stroke [7].

Estrogen, is a component of COCP. It is responsible for thrombogenic changes and alteration of coagulation factors which favors the formation of thrombi and consequently the possibility of triggering a stroke, and stroke risk is a possibility with any dosage [7].

Cochrane published meta-analysis showed that the risk of ischemic stroke was 1.6-fold increased in women using COCP. The risk was highest for pills containing more or equal to 50 μg of estrogen [8].

Conclusion

Management of acute vaginal bleeding may overlap in patients with or without bleeding disorders [9].

Our particular case seem to belong to a yet unclassified platelet disorders but preliminary testing is suggesting that it may be due to abnormality of function or abnormality of number. She has a brother who is 14 years old with platelets counts of about of 50 - 70 x 10^3/uL. This particular brother had a bone marrow sampling was done at the age of 2 years and this showed normal trilineage hematopoiesis and normal megakaryopoiesis number with orderly maturation.

Although the specific genetic defect in this family has not been identified but it will appear to be X linked? With variable penetrance although congenital amegakaryocytic thrombocytopenia or unknown aetiology or is also a differential diagnosis.

In majority of cases a careful evaluation of the family tree mapping affected and non-affected individuals needs to be carried out in addition to genetic studies to evaluate for rare or new mutations. In the investigation of a patient with menorrhagia and suspected bleeding disorder a careful family history may reveal affected family members as in our case.

Presentation to the gynaecology team is not unusual and bleeding disorders should be considered in the work up and investigation of a patient presenting with heavy bleeding especially at menarche.

Management should involve a multidisciplinary team who are experienced in the management of bleeding disorders as well as other relevant specialities. Therapy should include blood, blood products and any known specific therapy aimed at the treatment of any known deficiency.

In appropriate cases, hormonal therapy in the form of oestrogen, progestrogens as well as ablative methods and even hysterectomy may be considered but this was not appropriate in our case.

It should always be borne in mind during the management of such cases that bleeding itself as well as measures to control the bleeding may pose a threat of stroke.

Reported cases of such severe presentation with intractable bleeding during menstruation is rare in literature and management is fraught with difficulty especially when there is no response to well-known measures. Therapy itself may pose a significant risk of complication either from blood and blood products as well as unexpected complications from the pro coagulant effects of hormonal therapy like stroke.

The occurrence of ischaemic stroke in our patient was unfortunate but probably not preventable as her symptoms were so severe however it should always be borne in mind as a potential complication while using multiple agents to control bleeding.

Disclosure

The authors declared no conflict of interest.

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