CASE REPORT

CONGENITAL HYPOFIBRINOGENEMIA; AN UNEXPECTED CULPRIT OF BLINDNESS IN AN INFANT

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Background: Congenital hypofibrinogenemia is a rare haematological disorder in which the production of functional fibrinogen is impaired because of the inherited mutation. Hypofibrinogenemia affects the coagulation cascade leading to bleeding diathesis and one of its manifestations can be recurrent Vitreous haemorrhages, sometimes leading to irreversible loss of vision. Therefore, Hypofibrinogenemia must be included in the differential diagnosis of Vitreous haemorrhage, particularly in young children. We report a case of a four months old female infant who was brought by her mother to the unit since she was afraid that the child might be unable to see since she was not following things for the last one month. Her ophthalmologic examination revealed bilateral vitreous haemorrhages. Further workup for the cause of the bleeding confirmed the diagnosis of hypofibrinogenemia which was then managed accordingly.

Keywords: Fibrinogen; Hypofibrinogenemia; Missense mutation

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INTRODUCTION

Congenital hypofibrinogenemia is an autosomal recessive bleeding disorder characterized by congenital deficiency of plasma fibrinogen and an estimated incidence of 1–2 per million in the general population has been reported so far.[1] Since this disease is rare, limited data is available on the incidence of bleeding episodes. Also, prevalent clinical manifestations and treatment modalities are scarce.[2] The mainstay of treatment is mainly replacement therapy with Fresh frozen plasma, cryoprecipitate (cryo) and lyophilized fibrinogen concentrate, but there is limited knowledge on optimal dosages and target plasma levels. Thus, in order to fill this gap of knowledge, we report a case of an infant with an unusual manifestation of this disorder in the form of decreased vision.

CASE PRESENTATION

The patient is a four months old female infant brought by her mother to the emergency department with the suspicion of decreased vision over the past one month. She was born of consanguineous marriage and her past history was positive for episodes of prolonged umbilical cord bleeding during the 1st month of her life. Family history was not significant.

Physical examination was normal with no bruises or petechial haemorrhages over her body. Ophthalmological examination under general anaesthesia revealed bilateral vitreous haemorrhages.

Laboratory workup showed microcytic hypochromic anaemia with an Hb of 12.2 g/dl (Ref: 12–15 g/dL), a mean corpuscular volume of 60 fL (Ref : 80-100 fL), a reticulocyte count of 1% (Ref: 0.5–1.5%), a white blood cell count of 12x10^^9/L (Ref: 4–10 x 10^9/L), and a platelet count of 174x10^9/L (Ref: 150–400x10^9/L). She had a normal coagulation profile with Prothrombin time of 12 seconds (Ref: 11–14 sec) and activated thromboplastin time of 36 seconds (Ref: 20–40 sec). Her Haemoglobin electrophoresis was also normal. Factor 13 deficiency was also ruled out. Her fibrinogen level was 0.5 g/l (normal value 1.49–3.53 g/l). Her protein C levels were 80% (normal range is 70–140%). Ultrasonic B-scan of both eyes confirmed vitreous haemorrhages (Figure-1, 2). Computed tomography scan revealed CSF density lesions and chronic hematoma in the right temporo-occipital region of the brain. (Figure-3). A diagnosis of congenital hypofibrinogenemia was made on the basis of Haematological abnormalities.

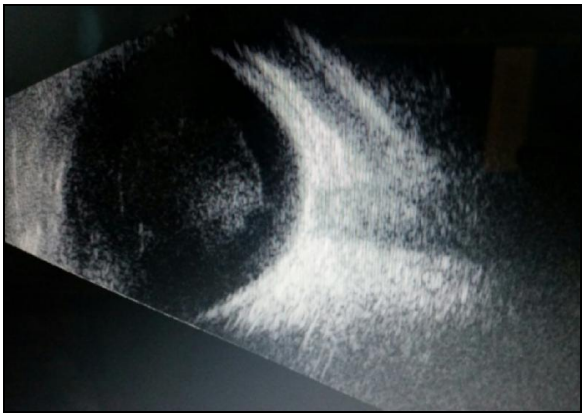

Figure-1: B Scan of the right eye showing dense vitreous haemorrhage

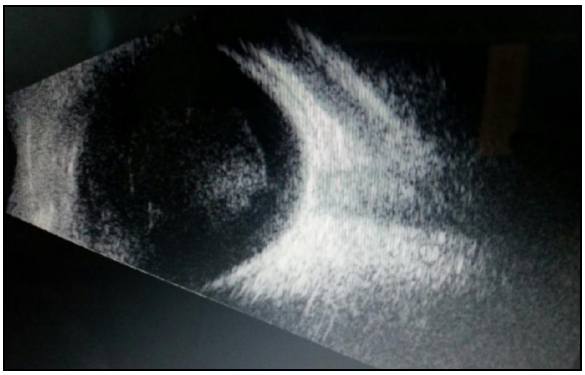

Figure-2: B Scan of the left eye showing vitreous haemorrhage

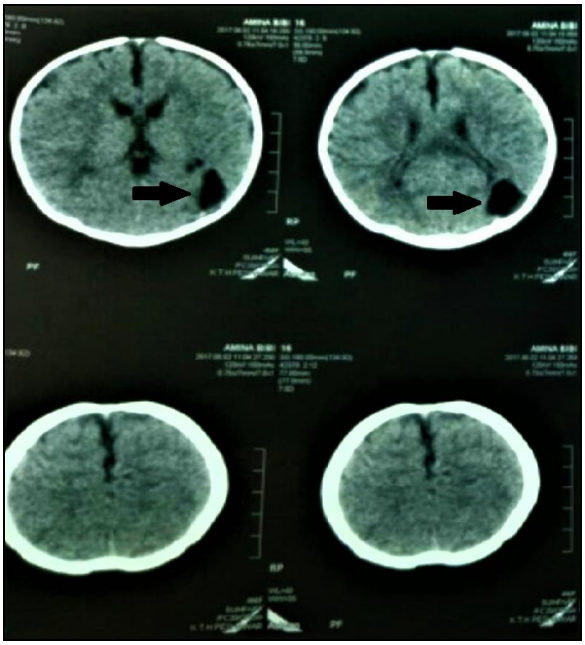

Figure-3: **CT brain showing CSF density lesion and chronic hematoma in the temporooccipital-region**

The patient was assessed by Haematologist who advised infusion of 3 units of cryoprecipitate of blood along with Vitamin K 10 mg daily for 1 month. After 3 days of cryoprecipitate infusion, her fibrinogen level was repeated and found to be within normal range, i.e., 2.63 mg/l. After 1-week repeat ophthalmological examination was carried out under general anaesthesia. The haemorrhage in the left eye had almost resolved while in the right eye she still had significant haemorrhage for which she was advised vitrectomy to prevent amblyopia but the parents refused surgery.

They were counselled regarding regular follow up at 2 months interval and lifelong FFPs or cryoprecipitate infusion when needed. They were advised to have regular blood fibrinogen level measurement and examination by Paediatrician and Haematologist along with a computed tomographic scan of the brain in the next visit to look for recovery of the hematoma. They were also offered Genetic counselling in case they wanted to have further babies.

DISCUSSION

This disease was described in 1920 with a prevalence of 1 in 1,000,000.[3] According to 2010 World Federation of Haemophilia annual global survey which included data from 106 countries, Hypofibrinogenemia accounts for 7% of all cases of bleeding disorders and is more common in females as compared to males.[4]

Congenital hypofibrinogenemia is a rare haematological disorder and approximately 250 cases have been reported worldwide until now.[5] Since it can cause recurrent ocular haemorrhages, it can, therefore, lead to irreversible blindness and thus it must be included in the differential diagnosis of paediatric ocular haemorrhages.

A chromosome 4 (q26–q28) association has been found in this disorder with homozygosity causing Afibrinogenemia (complete lack of Fibrinogen) and heterozygosity leading to Hypofibrinogenemia (subnormal levels of Fibrinogen). The deficiency of Fibrinogen (Factor 1) causes a disturbance in the coagulation cascade leading to recurrent bleeding anywhere in the body including the skin, oral cavity, gastrointestinal tract, genitourinary tract and central nervous system. The intracranial haemorrhage can be fatal. There can be a qualitative defect in fibrinogen which means the level of fibrinogen is normal, but it has abnormal function leading to haemorrhages. The combined defect which involves both quantitative and qualitative defect in fibrinogen is termed as hypo-dysfibrinogenemia. Afibrinogenemia is specifically an autosomal recessive disorder whereas Hypofibrinogenemia and Dysfibrinogenemia can have both autosomal recessive or autosomal dominant inheritance.[6]

Three cases have been reported in Literature where Ocular haemorrhages were observed in young patients secondary to Hypofibrinogenemia. Pathengay *et al* described bilateral visual loss from spontaneous Sub-hyaloid Haemorrhage in a 14 years old girl. Her coagulation profile was reported as normal but her fibrinogen level was measured 0.5 g/l and three months after the cryoprecipitate infusion her visual acuity completely recovered.[7] Marshman *et al* reported a 36 days old premature infant who presented with progressive bilateral retinal and vitreous haemorrhages and a fibrinogen level of 0.7 g/l.[8] Demir *et al* also observed a low

fibrinogen level in a 3 months old boy who underwent workup for bilateral leukocoria.[6]

Diagnosis is made by a specific test which includes measuring the blood fibrinogen levels. However, it must be kept in mind that low fibrinogen can be a sign of other diseases including liver and kidney disorders which must be excluded before the diagnosis of hypofibrinogenemia is made.

There are 3 different treatment options for factor 1 deficiency, i.e., fibrinogen concentrate, Fresh frozen plasma or cryoprecipitate infusion. After fibrinogen replacement therapy a common complication is intravascular blood clot formation for which treatment must be given beforehand.[6]

CONCLUSION

Congenital hypofibrinogenemia can have different presentations and is an extremely rare disorder but must be included in the differential diagnosis of ocular haemorrhages occurring at a very young age so that appropriate treatment can be done started immediately.

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