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# Congenital hyperferritinemia diagnosed in a 2 month old-A Case Report from India

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## Key words

Hyperferritinemia; iron overload; genetic hyperferritinemia; HHCS.

## List of Declarations

No authors declared any potential conflicts of interest. No funding and no ethical approval was required for this case report.The corresponding author is guarantor. All authors confirmed they have contributed to the intellectual content of this paper and have met the following requirements :(a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

## Running title

Congenital hyperferritinemia in 2 month old baby.

## Abstract

**Background:** In clinical medicine, ferritin is predominantly utilized as a serum marker of total body iron stores. In cases of iron deficiency and overload, serum ferritin serves a critical role in both diagnosis and management. Elevated serum and tissue ferritin are linked to coronary artery disease, malignancy, and poor outcomes following stem cell transplantation. Ferritin is directly implicated in less common but potentially devastating human diseases including sideroblastic anemias, neurodegenerative disorders, and hemophagocytic syndrome.
**Method:** We report a case of congenital hyperferritinemia with serum iron within reference range, along with bronchopneumonia, acyanotic congenital heart disease, anemia, hypocalcaemia and dysmorphism in a 2 month old baby. Symptomatic treatment was given.
**Result:** The baby was discharged after 7 days. In a stable condition and having gained some weight.He was diagnosed as a case of congenital hyperferritinemia as C reactive protein levels normalized but ferritin levels remained high and A37C mutation

within the iron-responsive element of L-ferritin was detected. He was born to consanguineous parents, there was history of cataract in the family and his mother also had high serum ferritin levels.
**Conclusion:** This case is an example of the detection of a rare genetic disorder in a child admitted with apparently innocuous symptoms of fever and inflammation. Our case underlines the importance of monitoring ferritin levels, along with other signs of inflammation in order to differentiate congenital hyperferritinemia from inflammatory cause.

## Introduction

It is well known that both acute and chronic inflammation, as occurring in infections, autoimmune disorders, chronic renal failure and cancer are associated with high ferritin levels. Another common process is cytolysis, an event that releases ferritin from the hepatocytes in patients with acute or chronic liver diseases. Very high levels of serum ferritin are found in Still's disease.
Hereditary hyperferritinemias are linked to mutations of three genes: the L-ferritin gene responsible for the hereditary hyperferritinemia cataract syndrome (without iron overload), the ferroportin gene leading to a dominant form of iron overload, and the ceruloplasmin (CP) gene corresponding to an iron overload syndrome with neurological symptoms.[ 1]

## Case

A 2 month old male baby was admitted with fever, cough and cold of 4 days duration and breathing difficulty since the past 2 days. He had bluish discoloration of the extremities. The child was apparently well till 4 days back when he developed cough and cold. He later developed breathing difficulty and poor feeding and was drowsy. There was no history of diarrhoea, convulsions or bleeding from any sites. He was irritable for the past 2 days with excessive crying. There was no history of rash, vomiting, photophobia, ear discharge and diarrhoea. Parents were consanguineous. He had no significant past history. There is history of asthma and cataract in the elderly members of the family. No definite history of cataract could be obtained in young children of the family.He was born normally at home, at term. There is no definite history suggestive of birth asphyxia or resuscitation. He was on breast feeds. He had been immunized for age.
Examination of the patient revealed a weight of 4.2 kg, heart rate of 176 per minute, respiratory rate 70 per minute. Oxygen saturation was 94 %. He was irritable with respiratory distress. All peripheral pulses were felt, he had pallor, but no cyanosis, oedema, clubbing or lymphadenopathy. The anterior fontanelle was at level. He had many dysmorphic markers, including triangular facies and flat occiput. Red reflex was absent.Eye examination showed lenticular opacities in both eyes. There were no neurocutaneous markers. He was using accessory muscles of respiration. There was no chest wall deformity. He had marked intercostals and sub costal retraction. The trachea was central. There was decreased air entry into lungs with extensive wheeze and crepitations.
Precordium was normal. The apex beat was felt in the left 5th intercostals space just medial to the mid clavicular line. The first and second heart sounds were normally heard. There were no murmurs or additional heart sounds heard. Abdomen was soft. The liver was felt 3 cm below the costal margin and spleen 2 cm below the costal margin. There were no other masses felt. Bowel sounds were normally heard. The child was drowsy and lethargic. He was irritable. The tone and power were normal in all four limbs. The deep tendon reflexes were normally elicitable. The spine was normal and there were no signs of meningeal irritation.

## Laboratory investigations were as under (reference ranges in parentheses)

At admission, his hemoglobin level was 7.5 g/dl [11-15.5 g/dl], red blood cell count 2.64 million/cumm [4.5-5.5 million/cumm], PCV 21.8% [45-50 %], erythrocyte sedimentation rate 50/mm 1st hour [5-15 1st hour], C-reactive protein (CRP) was 31.25 mg/L [upto 6 mg/L], calcium 6.7 mg/dl [8.4-10.2 mg/dl], phosphorus 8.5 mg/dl [2.5-4.5 mg/dl], total protein 5.5 gm/dl[6.5-8.1 g/dl], albumin 3.3 gm/dl [3.5-5g/dl]. Creatine phosphokinase was 247 U/L [33-186 U/L], lactate dehydrogenase 541 U/L [266-500 U/L], iron 79 ug/dl [45-182 ug/dl], total iron binding capacity 181 ug/dl [250-450 ug/dl], ferritin 4098 ng/ml [30-300 ng/ml] and transferrin saturation 43.6%[20-50 %].Serology for dengue, salmonella typhi and malaria were negative. Urinary calcium and PTH were not done.
On the second day, CRP was 11.38 mg/L [upto 6 mg/L] and calcium 7.8mg/dl. On 5th day in hospital, his CRP had fallen to less than 0.6 mg/dl, calcium was 8.9 mg/dl but ferritin levels were still high at 1760 ng/ml [30-300 ng/ml]. A37C mutation within the iron-responsive element of L-ferritin was detected in our case.No genetic studies of parents were possible as the patient was lost to follow up.

## Hospital course

The patient was brought with complaints of fever and irritability. He was haemodynamically stable. In view of the high fever and irritability, blood investigations and CSF for analysis was sent and he was started on appropriate antibiotics. The counts

showed leucocytosis and shift to the left with elevated CRP. His oxygen saturation remained normal. A CT scan of the brain was done which did not show any gross structural anomaly. The CSF analysis was done which was normal. The serum electrolytes and renal function were normal. Child had hypocalcaemia and so was started on calcium supplements.
The chest X-Ray showed bilateral patchy opacities.the antibiotics were continued and was planned to give for at least 7 days. Repeat count and CRP showed gradual decrease. The fever and irritability gradually decreased. As the blood and urine cultures were sterile, the antibiotics were planned to be given for 7 days. The child was tolerating feeds well. The IV fluids were tapered and stopped. He had a short ejection systolic murmur. An ECHO was done which showed a small ASD with left to right shunt. There was no evidence of cardiac failure. Urine microscopy showed few pus cells but the culture was sterile. Initial reports revealed microcytic hypochromic anaemia.The serum iron was normal. Serum ferritin was markedly elevated. The baby was diagnosed as a case of bronchopneumonia, with acyanotic congenital heart disease, anemia, hypocalcaemia and dysmorphism. Patient was treated with IV fluids, injectable antibiotics and calcium gluconate.
The baby was discharged after 7 days. At discharge, he was afebrile. Respiratory rate was 30 per minute, tolerating feeds. There were no seizures, vomiting or lethargy. The neonatal reflexes were normal. There were no focal deficits. Head circumference was 40 cm, length 59 cm, and weight 4.508 kg.
At follow up one week after discharge, the patient had calcium 8.9 mg/dl, CRP <0.6 mg/L [upto 6 mg/L] and serum ferritin 1006.9 ng/ml [30-300 ng/ml].Six months later,serum ferritin levels were 708 ng/ml.

## Discussion

Ferritin is a 24-subunit protein that is composed of two types of subunits, termed H and L. H refers to the original isolation of isoforms of ferritin from human heart, which are rich in the H subunit, or to its electrophoretic migration as the heavier of the two subunits. L refers to ferritin isolated from human liver, which is rich in a lighter subunit. The ratio of H to L subunits within the assembled ferritin protein varies depending on tissue type and developmental stage. Genes encoding the H and L subunits of human ferritin are located on chromosomes 11q and 19q respectively [2]
In our patient, the initial presentation of the child was with features of lower respiratory tract infection and sepsis, which can explain a gradual fall to 700 ng/ml of the serum ferritin as the child's condition improved. But soon after the sepsis cleared, the serum ferritin was inexplicably high.This led us to look at causes of hyperferritinemia not related to inflammation.
A rare dominant trait is hereditary hyperferritinemia/cataract syndrome (HHCS), first discovered in 1995, due to mutation in the Iron responsive element (IRE) element of the 5' untranslated region of L-ferritin mRNA. [3] The A37C mutation we found in our family had been previously reported in a paper that reviewd all 31 mutations (27 single nucleotide transitions and four deletions) described since 1995 [4].The mutation results in lack of repression of L-ferritin translation that becomes independent of iron availability and of iron regulatory protein regulation and occurs also in iron deficiency. Thus in HHCS, the high serum ferritin levels reflect an increased synthesis of the L-ferritin, but not of total body iron, since the L subunit does not participate in iron oxidation and storage. The condition is benign, the only clinical manifestation being early-onset bilateral cataract. Craig et al [5] mention a minimum prevalence of approximately 1/200000 for HHCS which could be an underestimate because serum ferritin level is not routinely measured by ophthalmologists investigating cataracts (including congenital cataracts), and there is generally a low awareness of the condition among ophthalmologists,and mutations reportedly exist that lead to lesser magnitudes of hyperferritinemia, which may result in clinically insignificant cataract [6] Kannengiesser et al.[7] reported a single novel mutation (p.Thr30Ile) in the coding sequence of L ferritin. This finding was remarkable because mutations of L ferritin are extremely rare and associated either with HHCS or a neurological disorder known as neuroferritinopathy
Beard et al [8] conducted a study on relationship of acute phase proteins to iron status biomarkers in infants and school children. They found that serum ferritin is the only biomarker of iron status that is consistently related to either CRP or α 1 acid glycoprotein.There is a documented case report of a 3 year old Italian boy with serum ferritin 1407 µg/L (normal values 20-300) with all the screening tests, including inflammatory markers being normal. There was family history of high ferritin levels and congenital cataract.The subsequent analysis of the promoter of the L ferritin gene showed the mutation A37C in heterozygosis in the child and in his mother [9] Bravo et al reported hyperferritinemia in a 3-month-old infant [10]
Other rare disorders are an autosomal dominant type A ferroportin disease, presenting with a low or slightly elevated transferrin saturation and tissue iron overload and some rare autosomal recessive disorders causing iron overload, aceruloplasminemia and atransferrinemia, Both disorders are characterized by microcytic anemia and variable transferrin saturations. Aceruloplasminemia or hypoceruloplasminemia have additional features such as diabetes and neurological symptoms, such as cerebellar ataxia, dementia or extrapyramidal symptoms. None of these disorders of iron metabolism are associated with congenital or juvenile nuclear cataracts, which is a unique feature of HHCS [11]

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