www.nephropathol.com DOI: 10.34172/jnp.2021.xx J Nephropathol. 2021;10(x):exx

Journal of Nephropathology

Neutropenia associated with proximal renal tubular dysfunction and mild bilateral cataract

Mitra Naseri[1*], Hamid Farhangi[2], Armin Attaran Zadeh[3], Zeynab Ghoroneh[1]

[1]Pediatric Nephrology Department, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Pediatric Hematology and Oncology Department, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Pathology Section, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article type:
Case Report

Article history:
Received: 10 November 2019
Accepted: 17 February 2020
Published online: 6 March 2020

Keywords:
Fanconi syndrome, Neutropenia, Cataract, Hypophosphatemic rickets, Fanconi syndrome

ABSTRACT

We report an 11-year-old girl admitted to nephrology section due to growth failure, neutropenia, renal glycosuria, and proteinuria and also hypophosphatemic rickets. She had a history of repeated hospitalization because of respiratory or gastrointestinal infections. Bone marrow aspiration revealed hyper-cellular bone marrow with mild dysplastic pattern. Eyes examination showed mild bilateral posterior cataract. X-ray of the wrist demonstrated a bone age of 3.5 ±6 months with evidence of rickets. We could not find a syndrome that can explain these associations.

Case Report

Implication for health policy/practice/research/medical education:
When encounter patients with chronic neutropenia and hypercellular bone marrow, systemic diseases with multi-organs (CNS, muscles, liver, joints and renal) involvements should be considered.

Please cite this paper as: Naseri M, Farhangi H, Attaran Zadeh A, Ghoroneh Z. Neutropenia associated with proximal renal tubular dysfunction and mild bilateral cataract. J Nephropathol. 2021;10(x):exx. DOI: 10.34172/jnp.2021.xx.

Introduction

Neutropenia is considered as a result of decreased bone marrow production, the sequestering or increased destruction of neutrophils in the peripheral blood. Congenital neutropenia includes a group of disorders associate either with permanent or intermittent neutropenia, and commonly accompanied by a combination of different organs involvement. The most involved organs include pancreas, central nervous system (CNS), heart, muscle and skin. Neutropenia is considered severe if there is an absolute neutrophil count (ANC) <500 cell /mm^3 or mild (ANC =500-1500 cell/mm^3). The risk of infection is high at neutrophil count <200 cell/mm^3 (1).

Kostmann' syndrome, an important cause of severe congenital neutropenia, firstly presents with hematologic manifestations, if the patients survive, neurological involvement in later years of the life will emerge (2). Fanconi syndrome, a tubulopathy with generalized proximal tubules dysfunction, is characterized by urinary losses of phosphate, uric acid, glucose, amino acids, low-molecular weight proteins and bicarbonate. It may be due to a mutation in sodium -phosphate transporter of the proximal tubular apical membrane (primary form) or secondary to inherited disorders including cystinosis, galactosemia, hereditary fructose intolerance, tyrosinemia, Lowe and Alport syndromes, Wilson's disease and mitochondrial disorders (3,4).

Case Presentation

An 11-year-girl (the 8th child of the family) admitted for assessment of growth failure, rickets, and abnormal hematologic and urinalysis findings. She had a history of repeated hospitalization due to febrile episodes associated with respiratory or gastrointestinal symptoms. Also in age of 6 years old she was admitted due to severe anemia

*Corresponding author: Mitra Naseri, Email: Naserim@mums.ac.ir

and had received packed cell transfusion. Laboratory tests at that time had reported as serum hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) of 6.4 g/dL, 60 fl, 15.5 pg, and 25.8 g/dL, respectively. White blood cells (WBC) count was 3300 cell/mm^3 (leukopenia), with an ANC of 600 cell/mm^3 (mild neutropenia), but platelets count was normal (340×10^3 cell/mm^3). Repeated CBC tests after discharge were conducted and leukopenia with an ANC of 500-1000 cell/mm^3 was a persistent finding. The CBC tests were recommended in infectious phases and also when the patient was asymptomatic.

Different urinalysis (U/A) tests during the past 5 years revealed trace to 3+ glycosuria with normal blood sugar levels (renal glycosuria) and mild proteinuria (trace to +). Serum levels of calcium (9.4 mg/dL), phosphorous (4.6 mg/dL), 25 hydroxyl vitamin D3 (by enzyme-linked fluorescent assay; ELFA, method = 95 ng/mL) and thyroid-stimulating hormone (TSH) were checked last year and all were in normal ranges.

Short stature (L=104 cm, Z score of -5.7), and body weight of 12.4 kg (Z score -8.6) were indicative of severe failure to thrive. Motor and mental development, muscles tonicity and force were normal. A heart rate of 90/min, respiratory rate of 24/min and blood pressure of 100/60 mm Hg were recorded at the time of admission. Abdominal distention without organomegaly or any palpable mass, bilateral genovalgus and widening of wrists (evidence of rickets) were the most important findings. Eyes examination with slit lamp reported mild bilateral posterior cataract with normal lens, retina and cornea. A bone age of 3.5 years ±6 months and bone changes consistent with rickets were reported on X-ray of the left wrist. Kidney and bladder ultrasonography (US) and chromosomal breakage test were normal. Laboratory investigation was done to evaluate the etiology of proximal renal tubular dysfunction and neutropenia (Table 1). Samples of bone marrow aspirates (BMA) determined a hypercellular bone marrow with mild dysplastic change in different cell lines, with a blast cells count of <5% (normal blast count at BMA). Final description for bone marrow aspiration was active bone marrow with mild dysplastic megakaryocytic changes (Figure 1A–1C).

Because the neutropenia was not severe and did not associate with bacterial infection, administration of prophylactic antibiotic or granulocyte colony-stimulating factor were not indicated. The patient received a single dose of vitamin D3 (300 000 IU), followed by administration of calcitriol 0.25 µg daily. Serum phosphorous level one week after treatment reached to 4 mg/dL. After discharge from the hospital patient lost follow up.

Discussion

Our case presented with evidence of incomplete Fanconi syndrome (short stature, hypophosphatemic rickets, renal glycosuria and tubular proteinuria) associated with neutropenia and bilateral mild posterior sub-capsular cataract. Hypercellualrity of bone marrow suggested neutropenia due to peripheral destruction. Different genetic syndromes present by neutropenia due to impaired bone marrow function (4-7). Neutropenia because of impaired bone marrow function is a common finding in Shwachman syndrome (81%). Association of neutropenia with diarrhea, as the classic presentation of the syndrome, is reported in about 50% of cases, also growth retardation (73%) and skeletal abnormalities (38%) are common (5).

The classic triad of abnormal skin pigmentation, nail dystrophy, and oral leucoplakia are the main presentations of dyskeratosis congenita, an inherited bone marrow failure syndrome (6). Bone marrow failure which is a leading cause for mortality occurs at age 30 years in 80-90% of cases. X-linked Barth syndrome usually diagnosed in infancy and "characterized by cardiomyopathy, skeletal myopathy, growth retardation, neutropenia and increased urinary excretion of 3-methylglutaconic acid (3-MGCA' (7).

Decrease in phagocytosis in Chediak-Higashi syndrome, a rare lysosomal storage disorder, which results in recurrent pyogenic infections. Albinism, bleeding diathesis, abnormal natural killer cell function, neutropenia, peripheral neuropathy and giant neutrophil granules are additional findings (8). Mitochondrial cytopathy can associate with hematologic systems involvement as sideroblastic anemia, neutropenia, and thrombocytopenia. The disease can affect all organs. Skeletal involvement and myopathy are common. "Ocular problems such as progressive external ophthalmoplegia, ophthalmoparesis, pigmentary retinal degeneration, ptosis, cataract, optic atrophy, and blindness can be seen in many patients. Renal involvement may present as tubulopathy, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, cystic kidney disease, myoglobinuria, or renal failure" (9). Serum lactate, urinary lactate and pyruvate concentrations are frequently elevated. About 1/3 of cases have overt Fanconi syndrome. Renal tubular involvement may present as proximal renal tubular acidosis, glycosuria, hyper phosphaturia, and/or aminoaciduria (9).

Clinical findings in our case were not consistent with diagnosis of congenital genetic syndromes associated with neutropenia or autoimmune neutropenia (an ANC <1500 /µL due to an immune-mediated process). Autoimmune neutropenia associate with anti-neutrophil membrane antibodies (ANA), directed against antigens located on the neutrophil cell surface (10). Large granular lymphocyte (LGL) leukaemia, systemic lupus erythematosus (SLE),

Table 1. Laboratory findings in our case

Laboratory tests	Findings (Normal ranges)
WBC count	3700 cell/mm^3 (4000-11000 cell/mm^3)
Differential neutrophil count	18% (40–80%)
ANC	666 cell/mm^3 (≥1500 cell/mm^3)
Hb	11.5 g/dL (12.0 to 15.5 g/dL)
Hct	40.3% (36 to 48 %.)
Platelet count	397000 cell/mm (150000-450000 cell/mm^3)
Serum LDH	420 U/L (140-280 U/L)
Serum creatinine	0.5 mg/dL
Serum urea	15 mg/dL
Serum sodium	138 meq/L (135-145 meq/L)
Serum potassium	4 meq/L (3.5-5 meq/L)
Serum calcium	8.8 (8.8-10.2) mg/dL
Serum phosphorus	2.4 mg/dL (4-5.2 mg/dL for ages 8-13 years)
Serum ALP	2882 (up to 1200) U/L
Serum PTH	14 pg/mL (15-65 pg/mL)
Serum 25 OH vitamin D	19 ng/dL (≥30 ng/dL)
Serum TSH (IRMA method)	2.1 mIU/mL (0.5 to 6.4 mIU/ml)
Serum free T4 (RIA)	8.1 µg/dL (4.5-11.8 µg/dL)
Fasting blood sugar	70 mg/dL) (≤100 mg/dL)
VBG analysis	pH=7.33, PCO2 =37.7 mm Hg, HCO3=20.2 mmol/L
Total protein	7.1 (6.0 to 8.3) g/dL
Serum albumin	4.1 (3.5-5.5) g/dL
Serum lactate	2mmol/L (up to 2 mmol/L)
ESR 1	31 (<15) mm/h
ANA (ELISA method)	1.7 U (≤1U negative,1.1-2.9 U weakly positive and ≤ 3 positive)
Serum IgG	750 mg/dL (639-1344 mg/dL)
Serum IgA	325 mg/dL (70-312 mg/dL)
Urinalysis (U/A)	SG=1006, pH=5, Protein =++, Sugar =+++ WBC=1-2, RBC=0-1
24-hour urine phosphorus*	263 mg/24 h (up to 15-20 mg/kg/d)
Urine amino acid chromatography (HPLC method)	Normal pattern
Wright and 2ME tests	Negative
SGOT	46 U/L (5 to 40U/L)
SGPT	30 U/L (7 to 56 U/L)
Urine 24-hour protein	668 mg/24h (≤150 mg/24 h)
Urinary 24-hour phosphate excretion	262.8 mg/d (>20 mg/kg/d)

WBC, White blood cells; ANC, absolute neutrophil count; Hb, hemoglobin; Hct, haematocrit; ALP, alkaline phosphatase; PTH, parathyroid hormone; TSH, thyroid stimulating hormone; VBG, venous blood gases; ANA, anti-nuclear antibodies; SGOT, serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic-pyruvic transaminase; ESR1, Erythrocyte sedimentation rate first hour.

Felty's syndrome [long-standing rheumatoid arthritis (RA) associates with chronic leukopenia, arthritis and splenomegaly], and toxic exposure (drugs) are main causes for secondary autoimmune neutropenia. However anti-neutrophil cytoplasmic antibodies (ANCA) target the neutrophil antigens, rarely positive ANCA or ANCA-associated diseases associate with neutropenia (10). Lack of clinical manifestations of RA or SLE, negative ANA and absence of lymphocytosis or BMA findings suggestive of LGL leukaemia were against the diagnosis of autoimmune neutropenia. Also there was no history of using drugs that associate with immune neutropenia (propylthiouracil, minocycline, hydralazine and levamisole). We did not check the serum ANCA levels, therefore ANCA associated neutropenia without underlying autoimmune disorders cannot be excluded.

Cyclic neutropenia; a rare autosomal dominant disorder; characterized by fluctuations in neutrophil count and neutropenia with 21-day periodicity lasts for 3–10 days (1). Mutations in the ELANE (ELA2) gene are responsible for the disease. As the patient had neutropeina in all CBC obtained in past 5 years, cyclic neutropenia was not a good diagnosis.

Macrocytosis due to ineffective or dysplastic erythropoiesis is a key finding in nutritional neutropenia (vitamin B12 or folate deficiencies). Large erythroblasts

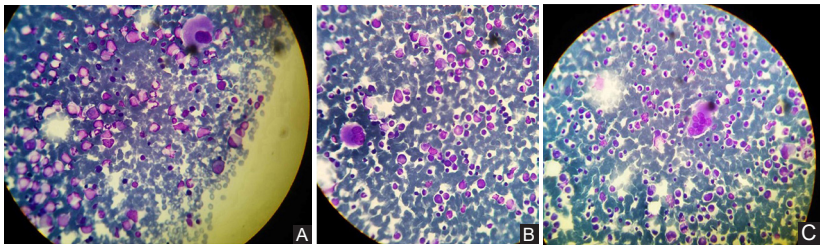

Figure 1. Microscopic examination of the bone marrow aspiration sample (Giemsa staining): Hypercellular bone marrow aspirate (A) with mild dysplastic pattern including hypolobulated nucleus and decreased peripheral platelet around megakaryocytes (B and C).

with nuclear/cytoplasmic asynchrony, hypercellular bone marrow with increased myeloid cells lines and dominancy of erythroid elements on bone marrow smears are other findings (11). However megaloblastic pancytopenia due to folate or vitamin B12 deficiencies occasionally presents with isolated neutropenia, macrocytosis with hyper segmented neutrophils, anisocytosis and polychromatic are the first abnormalities in peripheral blood smear (PBS) (12). Although we did not measure the serum or red blood cells levels of folate and vitamin B12, lack of macrocytosis in PBS and absence of ineffective erythropoiesis in BMA were negative points against diagnosis of nutritional neutropenia.

Cataract is an important component in Fanconi syndrome due to galactosemia, fructose intolerance and low syndrome. Lack of hypoglycemia, absence of neurologic symptoms, normal mental condition, female gender and normal serum transaminases levels were sufficient to rule out these diagnoses (Table 2). In addition, clinical presentations, laboratory and imaging findings were not consistent with diagnosis of Wilson disease, cystinosis, tyrosinemia, Dent's disease and Fanconi-Bickel syndrome (3,4).

Mitochondrial cytopathies were good initial diagnosis because of association of proximal renal tubulopathies and hematologic involvement. Renal tubulopathy and transient renal failure (more than 25% of patients) and overt Fanconi syndrome (1/3 of cases) are common (9). Hematologic findings consisted of anemia (mainly hypochromic and normocytic), thrombopenia, leukopenia (8.7% of cases) or eosinophilia. Due to high frequency of hematologic abnormalities, evaluation for mitochondrial cytopathy is recommended in children with unexplained cytopenia. Large cytoplasmic vacuolization of some bone marrow precursors is additional finding (13). Failure of organs with a high oxidative metabolic demand frequently seen, with predominance of brain and muscle dysfunctions. Renal involvement has been described as the first presentation of the disease which precedes encephalopathy (14).

The main hematologic presentations in our case were hypochromic microcytic anemia and neutropenia. As anemia was transient and disappeared after pack cell transfusion, it can be caused by iron deficiency. Unfortunately serum iron and ferritin levels were not checked before transfusion. Sideroblastic anemia did not suggest because of absence of ring sideroblast in BMA samples. The reasons against diagnosis of mitochondrial cytopathy included;

1. Normal serum lactate level, which is a common finding in mitochondrial cytopathy. This finding is so important that genetic studies were not recommended when serum lactate level is normal (9).
2. Lack of CNS and skeletal muscles involvements, the dominant manifestations of mitochondrial cytopathies, and non-progressive clinical course of renal and hematologic involvements (15).
3. Lack of external ophthalmoplegia and retinal pigmentary degeneration (15).

Considering major and minor criteria used for diagnosis of mitochondrial cytopathy (15). Our case had just evidence of two (renal and hematologic) organs involvement with sparing of the CNS and skeletal muscles. Recently biochemical and molecular genetic tests play an important role in diagnosis of mitochondrial cytopathy. Unfortunately these tests may not be available in most medical canters and are very expensive. Finally, we could not find a syndrome or a disorder that can explain association of severe growth retardation, proximal renal tubular dysfunctions and neutropenia in our patient.

Conclusion

The main messages found from this case report are as follows: (1) neutropenia is not a common etiology for recurrent infections, but it should be considered in differential diagnosis. (2) Obtaining a CBC examination and measurement of ANC when visiting a child with recurrent mucosal infections (respiratory and gastrointestinal) should be emphasized. (3) Renal tubulopathies as the etiology of growth retardation should be considered. (4) Complete evaluation of renal tubular function (U/A), measurement of serum electrolytes and arterial blood gasses) are recommended.

When encounter patients with chronic neutropenia

Table 2. A review of discussion

Study (reference)	Disorder	Key clinical findings	Key laboratories or imaging findings	Findings not match with our case
Starkebaum et al (10)	Immune-associated neutropenia	Different system involvement depends on underlying immunologic disorder	1) Positive ANA test (RA and SLE) 2) Lymphocytosis in peripheral blood smear and clonal cytogenetic abnormalities in bone marrow aspirate (LGL leukaemia) or positive ANCA	Negative ANA test, absence of lymphocytosis on PBS and BMA findings suggestive of LGL leukaemia
Aslinia et al (11)	Nutritional neutropenia	Symptoms of anemia	1) Macrocytic on PBS, large erythroblasts, hypercellularity of myeloid and erythroid elements on BMA 2) low levels of folate or vitamin B12 in serum and red blood cells	Lack of macrocytosis on PBS and ineffective erythropoiesis in BMA
Haque et al (3) Foreman et al (4)	Classic galactosemia, fructose intolerance	Growth retardation, vomiting and diarrhea, progressive neurologic symptoms	1) Evidence of hepatocellular damage 2) hypoglycemia 3) Evidence of Fanconi syndrome	Lack of hypoglycemia, absence of neurologic symptoms, presence of neutropenia
Haque et al (3) Foreman et al (4)	Low syndrome	Male gender, mental retardation, eye anomalies (mostly cataracts)	1) Fanconi-like proximal tubulopathy 2) mutations in the *OCRL* gene	Female gender, normal mental development
Haque et al (3) Foreman et al (4)	Cystinosis	Growth retardation, polyuria, Photophobia and visual impairment	1) Increased cysteine levels in leukocytes or skin fibroblasts 2) Corneal cystine crystal in split lamp examination	Normal renal function, presence of neutropenia and absence of cysteine crystal in cornea
Haque et al (3) Foreman (4)	Tyrosinemia	Hepatic failure with renal and CNS involvement	1) Laboratory evidence of acute liver failure 2) Fanconi-like proximal tubulopathy and renal dysfunction	Normal renal function, absence of hepatic failure and presence of neutropenia
Haque et al (3) Foreman et al (4)	Wilson's disease	Liver and neuro-psychiatric manifestations, Kayser-Fleischer rings in split-lamp examination	1) Abnormal liver function tests 2) Increased serum and urinary levels of copper 3) Fanconi-like proximal tubulopathy	Absence of hepatic or neuro-psychiatric manifestations and presence of neutropenia
Haque et al (3) Foreman et al (4)	Den's disease	Male gender, nephrolithiasis and progressive renal failure	1) nephrocalcinosis and nephrolithiasis on kidney US 2) Laboratory findings of renal failure	Absence of nephrocalcinosis and nephrolithiasis, female gender, normal renal function and presence of neutropenia
Haque et al (3), Foreman et al (4)	Fanconi-Bickel syndrome	Growth retardation, hypoglycemia and rickets	1) severe glycosuria and hypoglycemia 2) Fanconi-like proximal tubulopathy	Lack of hypoglycemia, presence of neutropenia
Kuwertz-Bröking et al (14) Challa et al (15)	Mitochondrial cytopathies	CNS and skeletal muscles involvement, progressive course, retinal degeneration and external ophthalmoplegia	1) High Serum lactate level 2) Specific molecular genetic testing 3) specific findings on muscle biopsy	Normal Serum lactate level, lack of CNS, skeletal muscles, retinal involvement and external ophthalmoplegia

ANA, anti-nuclear antibodies; LGL, large granular lymphocyte leukaemia; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; ANCA, anti-neutrophil cytoplasmic antibodies; PBS, peripheral blood smear; BMA, bone marrow aspirates; US, ultrasonography; CNS, central nervous system.

and hypercellular bone marrow, systemic diseases with multiorgans (CNS, muscles, liver, joints and renal) involvements should be considered.

Authors' contribution

MN; initial draft, and preparing the final manuscript. HF; involved in writing the discussion section. AAZ; biopsy images. ZG; gathering the patient information. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Schwartzberg LS. Neutropenia: Etiology and Pathogenesis. Clin Cornerstone. 2006;8 Suppl 5:S5-11.
2. Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. Orphanet J Rare Dis. 2011; 19(6):26. doi: 10.1186/1750-1172-6-26.
3. Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. Nephrol Dial Transplant. 2012;27(12):4273-87. doi: 10.1093/ndt/gfs493.
4. Foreman JW . Fanconi Syndrome. Pediatr Clin North Am. 2019;66(1):159-167. doi: 10.1016/j. pcl. 2018.09.002.
5. Myers KC, Bolyard AA, Otto B, Wong TE, Jones AT, Harris RE, et al .Variable clinical presentation of Shwachman-Diamond syndrome: update from the North-American Shwachman-diamond syndrome registry. J Pediatr. 2014; 164(4):866-70. doi:10.1016/j.jpeds.2013.11.039.
6. Nelson ND, Bertuch AA. Dyskeratosis congenita as a disorder of telomere maintenance. Mutat Res. 2012;730(1-2):43-51. doi: 10.1016/j.mrfmmm.2011.06.008.
7. Clarke SL, Bowron A, Gonzalez IL, Groves SJ, Newbury-Ecob R, Clayton N, et al. Barth syndrome. Orphanet J Rare Dis. 2013;8:23.doi: 10.1186/1750-1172-8-23.
8. Gil-Krzewska A, Wood SM, Murakami Y, Nguyen V, Chiang SCC, Cullinane AR, et al. Chediak-Higashi syndrome: Lysosomal trafficking regulator domains regulate exocytosis of lytic granules but not cytokine secretion by natural killer cells. J Allergy Clin Immunol. 2016; 137(4):1165-1177. doi: 10.1016/j.jaci.2015.08.039.
9. Emma F, Montini G, Salviati L, Dionisivici C. Renal mitochondrial cytopathies. Int J Nephrol. 2011; 2011:609213. doi: 10.4061/2011/609213.
10. Grayson PC, Sloan JM, Niles JL, Monach PA, Merkel PA. Antineutrophil cytoplasmic antibodies, autoimmune neutropenia, and vasculitis. Semin Arthritis Rheum. 2011; 41(3):424-33. doi: 10.1016/j.semarthrit.2011.02.003.
11. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. Clin Med Res. 2006;4(3):236-41.
12. Larke V, Weston-Smith S. Severe folate-deficiency pancytopenia. BMJ Case Rep. 2010;2010.doi: 10.1136/bcr.03.2010.2851.
13. Bader-Meunier B, Miélot F, Breton-Gorius J, Cramer E, Guichard J, Landrieu P, et al . Hematologic involvement in mitochondrial cytopathies in childhood: a retrospective study of bone marrow smears. Pediatr Res. 1999;46(2):158-62.
14. Kuwertz-Bröking E, Koch HG, Marquardt T, Rossi R, Helmchen U, Müller-Höcker J, et al. Renal Fanconi syndrome: first sign of partial respiratory chain complex IV deficiency. Pediatr Nephrol. 2000;14(6):495-8.
15. Challa S, Kanikannan MA, Murthy JM, Bhoompally VR, Surath M. Diagnosis of mitochondrial diseases: clinical and histological study of sixty patients with ragged red fibers. Neurol India. 2004;52(3):353-8.