Global Advanced Research Journal of Medicine and Medical Science (ISSN: 2315-5159) Vol. 3(10) pp. 275-280, October 2014
Available online http://garj.org/garjmms/index.htm

Case Report

A Rare Case of Classic Homocystinuria with Hyperpigmentation

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Accepted 20 October, 2014

An eleven years old girl was admitted to paediatric ward, at Omdurman Military Hospital, Khartoum, Sudan, with generalized skin hyperpigmentation, mental retardation and ectopia lentis. She was diagnosed as a case of classic homocystinuria (type I) with megaloblastic anaemia. Vitamin B12 and folicacid levels should be monitored periodically, in patients with classic homocystinuria.

Keywords: Homocystinuria, Hyperpigmentation, Megaloblastic anemia, Vitamin B_{12}, Folic acid.

INTRODUCTION

Classic homocystinuria (Type I) is an autosomal recessively inherited defect in transsulphuration pathway of methionine caused by deficiency of cystathionine β-synthase (CBS) which converts homocystine to cystathionine. It is the most common inborn error of methionine metabolism, characterized by ectopia lentis, mental retardation, psychiatric and behavioral disorders, skeletal abnormalities and thromboembolic episodes. Normally, most homocysteine, an intermediate compound of methionine degradation, is remethylated to methionine. This methionine – sparing reaction is catalyzed by the enzyme methionine synthase, which requires a metabolite of folic acid (5-methyltetrahydrofolate) as methyl donor and a metabolite of vitamin B_{12} (methylcobalamin) as a cofactor (Rezvani and Rosenblatt, 2011). Homocystinuria may result from defects in methylcobalamin formations (Type II), characterized by megaloblastic anaemia, homocystinuria, homocystinaemia and hypomethioninaemia. Deficiency of the enzyme methylenetetrahydrofolate reductase results in homocystinuria (Type III), which is characterized by homocystinuria, homocystinaemia and hypomethioninaemia. Individuals with CBS deficiency have been detected by routine screening of newborns for hypermethioninaemia with an overall frequency of 1 in 344,000 live births. Striking regional differences are present (Mudd et al., 1995). Typically patients with type I homocystinuria don't have megaloblastic anaemia and have high serum methionine levels. We here report a case of classic homocystinuria (type I) and describe two unusual or rare manifestation, megaloblastic anaemia and skin hyperpigmentation.

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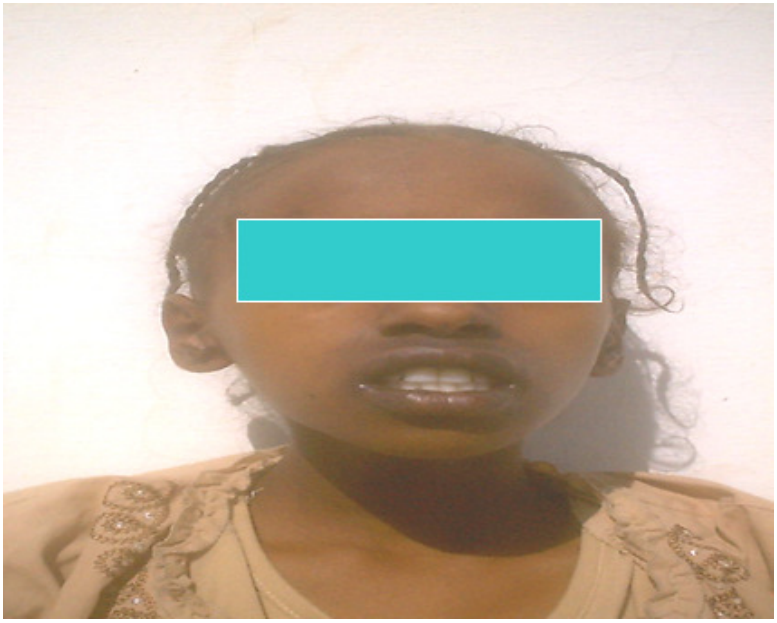

Figure 1. Perioral Hyperpigmentation

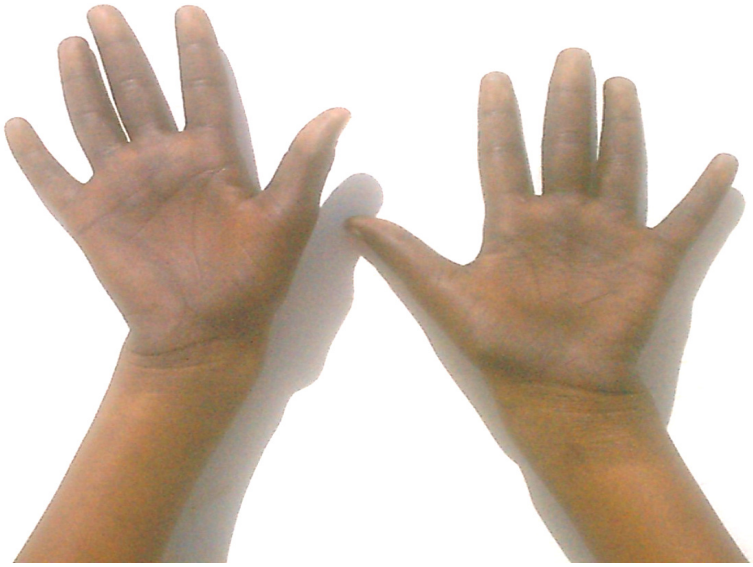

Figure 2. Hyperpigmentation in hands

CASE REPORT

The child was admitted to Omdurman Military Hospital to investigate a generalized skin hyperpigmentation for the last 4 years. It appeared, firstly, at tips of fingers and toes, then, involved palms and soles. Next, on tongue, lips and periorally, spread to axillae and genitalia. Lastly, trunk and thighs were affected. Hyperpigmentation was noticed to be darker during any illness and lighter after resolution. (see Figure 1-6)

The patient was delivered normally at Military hospital and started to suffer from general ill health from the second year of life. She had developmental retardation and defective vision which became obvious when she joined a mainstream school.

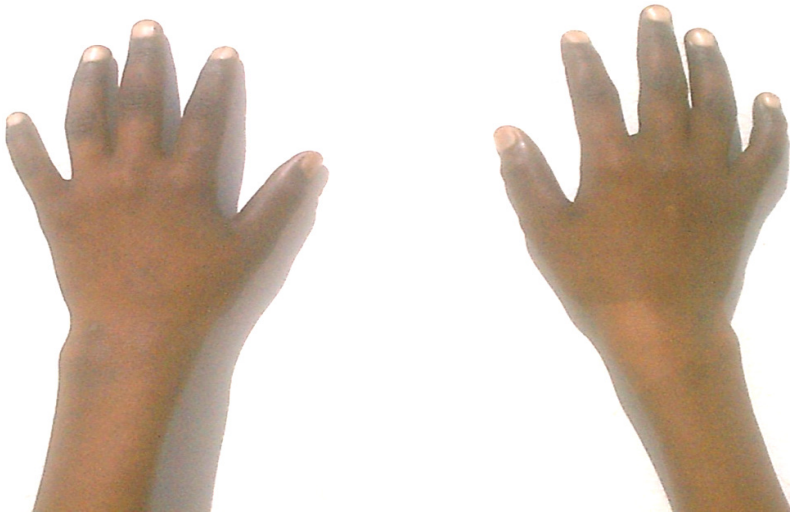

Figure 3. Hyperpigmentation in hands

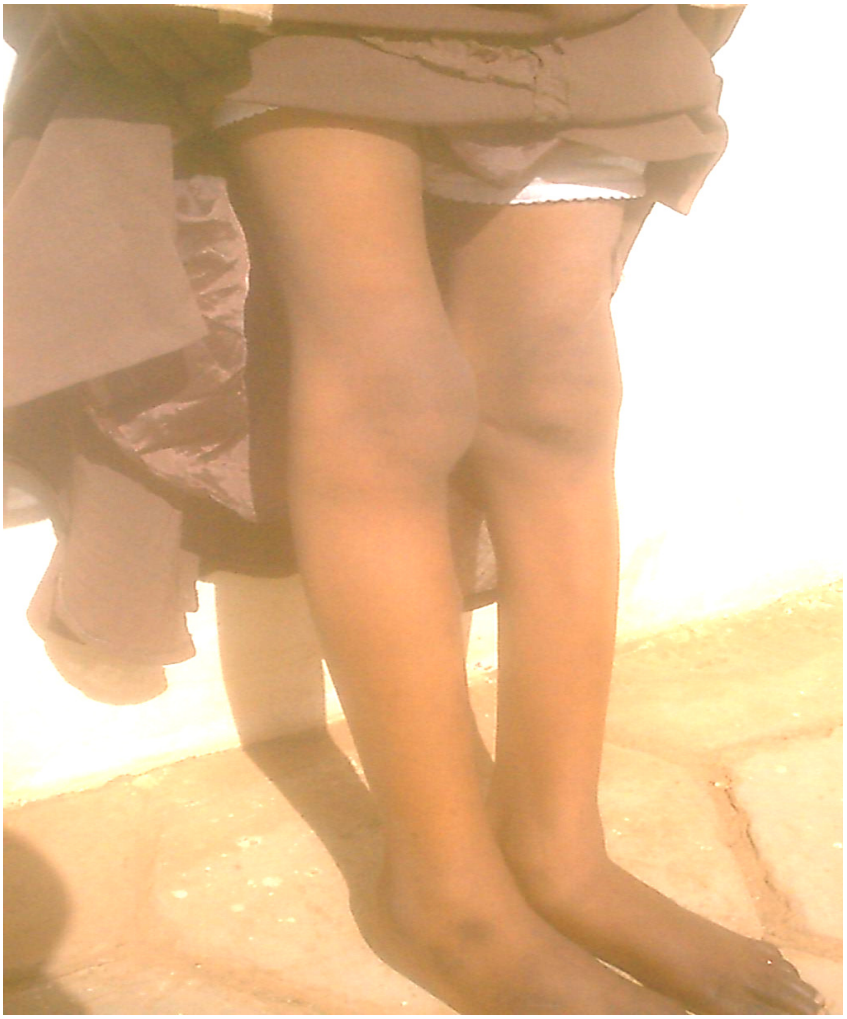

Figure 4. Hyperpigmentation in legs and feet

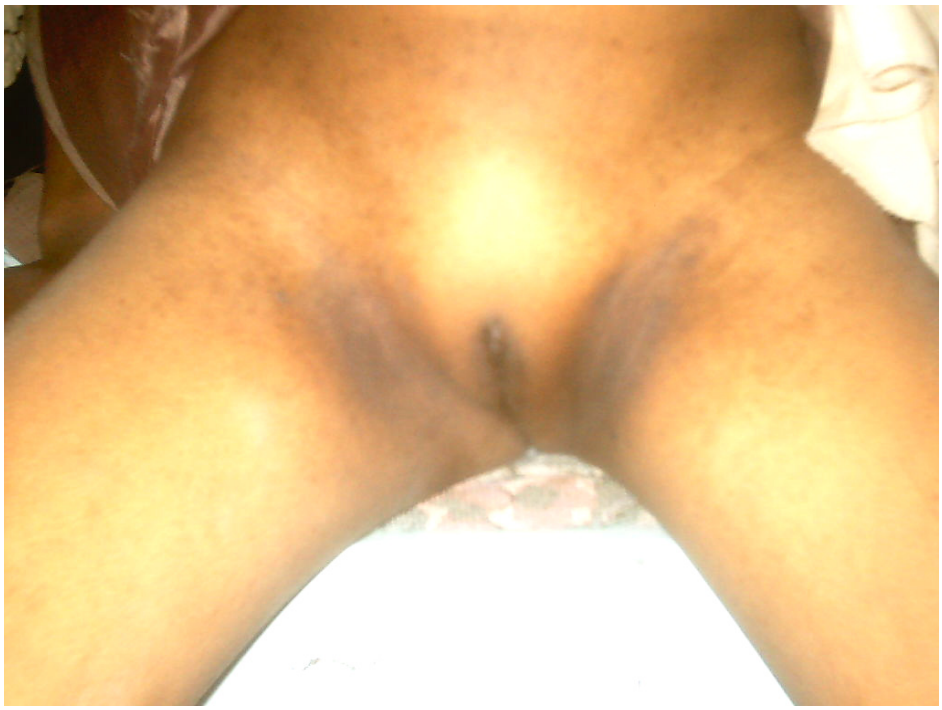

Figure 5. Hyperpigmentain around genitalia

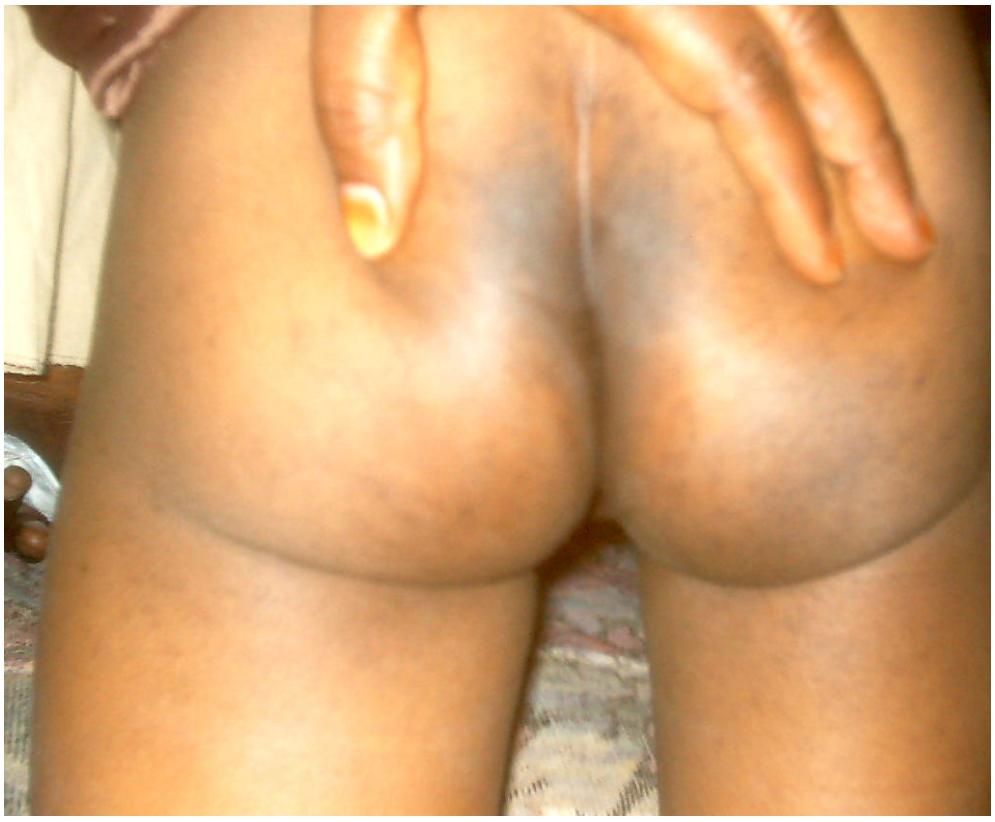

Figure 6. At buttocks

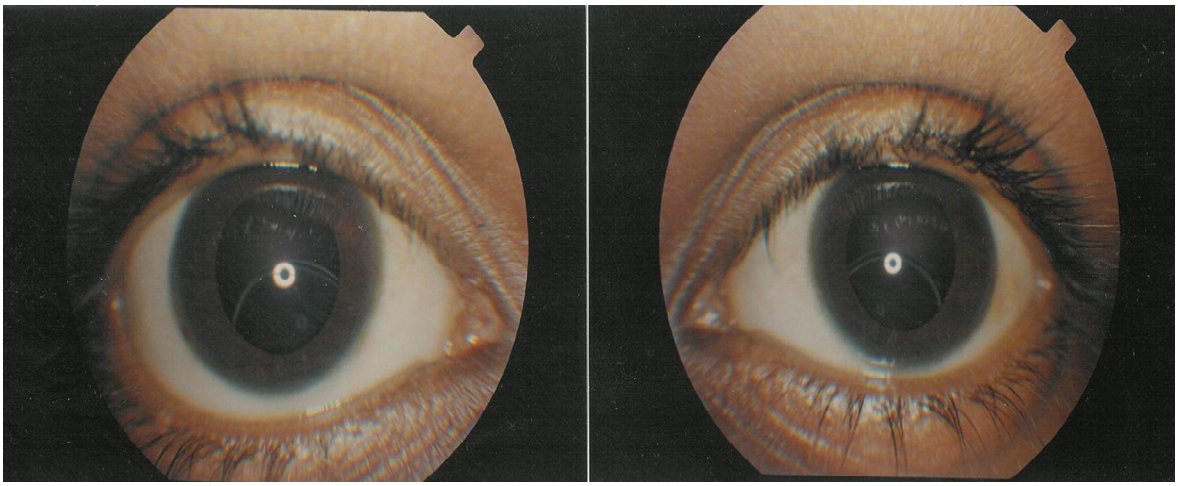

Figure 7. Both lenses were subluxated downwards and inwards

Physically, she is under weight, 32 kg, <25th. Centile, height 138 cm at 50th. Centile, head circumference 55 cm, >50th. Centile. Arm span/ height ratio 1.13, upper segment/lower segment ratio 0.97. Pulse 90/min regular not collapsing, blood pressure 100/60. She was pale not jaundiced, no dysmorphic features. She had short, dry, brittle sparse hair. Cheilosis and scaly dermatitis at nasolabial folds. She had bilateral cataracts and both lenses were subluxated downwards and inwards. (see Figure 7) Fundi were normal and no optic atrophy. There is high palatal arch, archnodactyl with positive wrist and thumb signs. There is no kyphosis or scoliosis, no joints laxity, stiffness or deformities. Cranial nerves were intact and no neurological deficit. She had moderate mental retardation with an I.Q. of 48on Stanford Binet Intelligence Scale.

Investigations revealed Haemoglobin of 8.6 g/dl, Hct 24%, RBC 2.0 x 10^6/ul, MCV 120.0 fl (NR 77 – 95), MCH 43.0 pg/cell (NR 25 – 33), MCHC 35.8 g/dl, TWBC 9.7 x 10^3/ul with normal differential. Peripheral blood film showed anisocytosis, oval macrocytes with hypersegmented neutrophils. Platelets were normal, 371 x 10^3/ul (NR 150 – 400).

Bone marrow aspiration showed hypercellularity with frank megaloblastic cells and giant metamyelocytes. Cyanide nitroprusside test was positive. Both urine and plasma were analyzed for amino acids using amino acid analyzer (Sykam 443). Urine examination with High Performance Liquid Chromatography (HPLC) revealed high levels of homocystine 88 umol/l (normally undetectable), methionine 142 umol/l (NR 7-20) with normal cystine level 17 umol/l (NR 11-53). Plasma amino acids analysis using HPLC showed high levels of homocystine 212 umol/l (NR 0-13), methionine 1225 umol/l (NR 13-30) and normal level of cystine 20 umol/l (NR 19-47). Methylmalonic acid< 1.0 umol/l (NR up to 1.0). Serum vitamin B_{12}89.21 pg/ml (NR 191-633), Folic acid 6.4 ng/ml (NR 4.8-37.3), pyridoxine (B_6) 121 pg/ml (NR 110-250). No facilities for enzymatic assay or molecular genetics. Urine and plasma amino acids analysis for parents and two sibs showed normal homocystine and methionine levels.

Accordingly, our patient was diagnosed as a case of classic Homocystinuria (Type I) with megaloblastic anaemia due to vitamin B_{12} and/or folate deficiency.

Treatment with vitamin B_{12} 1mg/day and folic acid 5mg/day, orally, for four weeks, resulted in complete disappearance of hyper pigmentation and normalization of blood picture. Hb.12.7 g/dl, Hct 35.9%, RBC 4.1x10^6/ul, MCV 87.8 fl, MCH 31.1 pg, MCHC 35.4 g/dl, TWBC 4.7 x10^3/ul, platelet count 251 x10^3/ul. retic count 0.2%. Normal cells morphology and differential. Pyridoxine challenge test, after correction of megaloblastic anaemia, with doses as high as 1g/day of pyridoxine failed to lower the plasma and urine homocystine. Patient was declared a pyridoxine resistant and advised to avoid diet rich in methionine.

Patient was lost to follow up for almost 3 years to present again with similar previous picture. This time after correction of her anaemia and hyper pigmentation she was kept on oral prophylactic doses of folic acid 2.5 mg/every other day and vitamin B12 500 µg/every other day. Follow up of the patient, no further anaemia or hyper pigmentation developed. Biannually check of serum levels of vitamin B12 and folic acid remained within reference range.

DISCUSSION

In our opinion, this patient is a case of classic homocystinuria (type I) due to; homocystinaemia, methioninaemia, homocystinuria, methioninuria, with lower normal cystine levels. Megaloblastic anaemia is due to vitamin B_{12} and/or folic acid deficiency, as a result of excessive utilization of vitamin B_{12} and methyltetrahydrofolate in the passway of remethylation of homocysteine to methionine (Ishida et al., 2001). Homocystinuria is usually associated with hypopigmentation due to inhibition of tyrosinase, the major pigment enzyme (Baloghova et al., 2013). Cutaneous manifestations associated with vitamin B_{12} deficiency are skin hyperpigmentation, vitiligo, angular stomatitis, and hair changes (Kannanand Joo, 2008; Wadhwani et al., 2012). In our patient, hyperpigmentation was most probably due to vitamin B_{12} deficiency, suggested by the pattern of distribution of hyperpigmentation, low serum level of vitamin B_{12} and supported by the dramatic response to the vitamin B_{12} supplement (Baker et al., 1963). Predominant mechanism of hyperpigmentation in vitamin B_{12} is hypothesized as: [i] Deficiency of vitminB_{12} decreases the level of reduced glutathione, which activate tyrosinase and thus leads to transfer to melanosomes. [ii] Defect in the melanin transfer between melanocytes and keratinocytes, resulting in pigmentary incontinence. In this case the dominant mechanism of hyperpigmentation could be a defect in melanin transport rather than an increase in melanin synthesis (Baloghova et al., 2013; Agrawala et al., 2013; Mori et al., 2001). The association between hyperpigmentation and vitamin B_{12} deficiency is known (Baker et al., 1963; Agrawala et al., 2013; Srivastava et al., 2006). The association between classic homocystinuria (type I) and megaloblastic anaemia are very rare, worldwide, only three cases are reported. (Ishida et al., 2001; Sunil et al., 2004; Bhardwaj et al., 2010). None of the three reported cases had hyperpigmentation. We recommend to check serum levels of vitamin B_{12} and folate in patients with homocystinuria type I and to consider their prophylactic administration.

ACKNOWLEDGEMENT

We acknowledge the central laboratory, ministry of science and communications for technical assistance.

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