previously reported: bilateral microspherophakia and probably bilateral ectopic lenses. It should be noted, however, that the proband's congenital nuclear cataracts were inherited from his mother and may have no connection with the syndrome. According to the pedigree (fig 1), the cataracts appeared for the first time (de novo) in the maternal grandmother, who transmitted it to all her children by a presumed autosomal mode of inheritance.

The proband had a positive 'methacholine test', which is considered by Howard³ to be "specific in establishing the diagnosis in the cri-du-chat syndrome". This reaction of the pupil to methacholine, in addition to its considerable resistance to mydriatics, suggests a possible defective structure of the dilator muscle of the pupil in our proband.

The proband's 5p- was transmitted from the mother who is a balanced translocation carrier (5p;13q). This is the fourth familial cri-du-chat case to be reported with a translocation involving the short arm of chromosome 5 and the long arm of chromosome 13.⁵ The total frequency of familial cri-du-chat cases is 12.1%, out of which 11.2% is the estimated frequency of familial translocation.

Cytogenetic investigation of the proband's maternal relatives in three generations showed that

the translocation 5;13 in the mother was de novo. The normal karyotypes observed in her relatives with cataracts exclude any relationship between the chromosomal defect and the cataracts.

The authors thank the medical and nursing staff of the Neonatal Unit of the Second Department of Pediatrics for their help and co-operation, and Miss Maria Kouvari for her skilled laboratory assistance.

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Correspondence and requests for reprints to Dr Sofia Kitsiou-Tzeli, 51 Kousidou Street, Athens 624, Greece.

Phenazopyridine induced methaemoglobinaemia associated with decreased activity of erythrocyte cytochrome *b₅* reductase

JENNIFER S DALY, DONALD E HULTQUIST, AND DONALD L RUCKNAGEL

Departments of Internal Medicine, Biological Chemistry, and Human Genetics, University of Michigan Medical Center, Ann Arbor, Michigan 48109, USA.

SUMMARY A 25-year-old woman taking usual doses of phenazopyridine developed her third clinically significant episode of cyanosis. Life threatening methaemoglobinaemia was documented and was treated with methylene blue. The patient and several members of her family showed decreased activities of erythrocyte NADH-cytochrome *b₅* reductase, predisposing them to the development of clinically significant methaemoglobinaemia when challenged with oxidant drugs.

Phenazopyridine is a commonly used urinary

analgesic. Methaemoglobinaemia is a rare side effect of the drug, first reported by Crawford *et al*¹ in 1951 in an infant. Since then 11 cases have been reported, most associated with ingestion of many times the usual therapeutic dose. Only two cases have been reported with standard dosages,² and these occurred in patients with mild renal insufficiency. In none of the reported cases has an abnormality of erythrocyte cytochrome *b₅* reductase (NADH-methaemoglobin reductase) activity been documented. Decreased activity of this enzyme has been reported in subjects who are especially susceptible to toxic methaemoglobinaemia secondary to ingestion of oxidant drugs.^{3,4} We report a case of life threatening methaemoglobinaemia in a patient with decreased reductase activity after ingestion of near-therapeutic amounts of phenazopyridine.

Received for publication 13 October 1982.
Accepted for publication 11 November 1982.

Case report

A 25-year-old white nurse (II-1, figure) was admitted to Wayne County General Hospital because of cyanosis and confusion. The patient had a history of dysuria for 5 days and had begun self medication with phenazopyridine (200 mg orally four times daily). She denied ingesting any larger amounts of the medication and was taking no other drugs. The patient became dizzy and was noted to be blue when she reported to work. Past medical history revealed several previous urinary tract infections treated with antibiotics, and on some occasions she had taken phenazopyridine without previous complications. She had had an episode of cyanosis diagnosed as 'respiratory arrest' requiring intubation after taking sulpha drugs at the age of 2 and during an abdominal angiogram at the age of 23.

On arrival in the emergency room the patient was lethargic and her skin was slate blue despite administration of 5 l/minute of oxygen by nasal cannula. Blood pressure was 120/70 mmHg, pulse 120, and respiratory rate 12 per minute. Her conjunctivae were brown and lips, nails, and sclerae were dusky blue. The patient's blood was chocolate coloured and did not become red with shaking in air. One drop of 10% potassium cyanide changed the colour of the blood from chocolate to red. Arterial blood was pH 7.44, P_{O_2} was 139 mmHg, P_{CO_2} was 30 mm, and O_2 saturation was 99% while breathing 50% oxygen. Haemoglobin was 15.0 g/dl and creatinine 0.9 mg/dl. G6PD level was normal. Urine analysis showed pyuria and bacteriuria.

The patient was given 90 mg of methylene blue (1.5 mg/kg) intravenously in a 1% solution over 10 minutes. Within 20 minutes the patient became more alert and there was a dramatic improvement of her dusky discolouration. Methaemoglobin level, which was 53.5% on arrival in the emergency room,

was 2.4% a few hours later, and 3.3% on the morning after admission.

The haemoglobin electrophoretic pattern on cellulose acetate was normal. The possibility that she had an unstable haemoglobin variant was excluded by the thermal denaturation test.⁵

The patient and several members of her family were evaluated for erythrocyte NADH-cytochrome b_5 reductase levels. The reductase was assayed photometrically using dichlorophenolindophenol (DCIP) as electron acceptor.⁶ DCIP reduction was corrected for the non-enzymatic reaction, normalised on the basis of haemoglobin concentration, and reported as a percentage of a normal control. Assays were performed several times by different laboratory workers. The DCIP reductase activity of the patient was 72% of normal. Several of her family members also showed abnormally low levels (figure). The NADH-cytochrome b_5 reductase level was also shown to be abnormally low in erythrocytes from her brother when methaemoglobin-ferricyanide was used as electron acceptor.⁷ With this electron acceptor, the enzyme showed a normal apparent K_M for NADH (approximately 5 μ mol/l).

Discussion

The normal pathway for reduction of methaemoglobin is initiated by cytochrome b_5 reductase which catalyses the reduction of cytochrome b_5 . The reduced cytochrome b_5 then transfers an electron non-enzymatically to methaemoglobin.⁸ The patient and several members of her family showed activities of reductase which were less than that of controls. In the DCIP assay methaemoglobinaemic patients with homozygous deficiency of reductase usually show an activity of about 10% of normal, while their heterozygous (and non-cyanotic) relatives have activities of approximately 55% of normal. Although the range of expression among affected persons is inexplicably large, we conclude that the patient and three of her family members are heterozygotes for a variant reductase with some, but not full, activity under DCIP assay conditions.

Acquired toxic methaemoglobinaemia has been associated clinically with a variety of drugs and chemicals. Levels of methaemoglobin above 10% cause clinically recognisable cyanosis. Lethargy and confusion occur at levels above 30%. Levels above 70% have been lethal.⁹ The diagnosis is suspected clinically when cyanotic patients, with no history of pulmonary or cardiac disease, do not respond to oxygen. The blood has a peculiar chocolate colour and does not become red on shaking in air. The addition of KCN produces a red colour (cyanmethaemoglobin) differentiating methaemoglobin

FIGURE Erythrocyte cytochrome b_5 reductase levels in the patient's family. The reductase was assayed using DCIP as electron acceptor. Results are reported as percentage of normal. Arrow denotes proband.

from sulphhaemoglobin. An effective antidote, methylene blue, allows methaemoglobin to be reduced by a NADPH-dependent reductase system. Ascorbic acid and riboflavin can be used to reduce methaemoglobin in the homozygous deficiency but do not act rapidly enough to aid in the emergency management of acquired toxic methaemoglobinaemia.

The case reported illustrates a life threatening toxic reaction to a commonly used urinary analgesic. This was the third episode of drug induced cyanosis in the patient. This case provides further evidence that oxidant drugs place heterozygotes (as well as homozygotes) for the deficiency at risk of significant methaemoglobinaemia.¹⁰

We wish to acknowledge the role of Mr Stephen Maassen, Mr Timothy Mather, and Dr David Juckett in the determination of cytochrome *b₅* reductase levels, and thank Floretta Reynolds for the haemoglobin studies and Mary Kellogg for secretarial assistance. This work was supported in part by USPHS Research Grants AM-09250 and AM-20964.

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Correspondence and requests for reprints to Dr Donald E Hultquist, Department of Biological Chemistry, Medical Sciences Building I, Box 034, University of Michigan, Ann Arbor, Michigan 48109, USA.

Involvement of dorsal root ganglia in Fabry's disease

NATAN GADOTH AND URI SANDBANK

Departments of Neurology and Pathology, Beilinson Medical Center, Petah Tiqva, Tel Aviv University Sackler School of Medicine, Israel.

SUMMARY Bouts of shooting pain along the extremities are common in the early stages of Fabry's disease. No pathological explanation has been advanced to clarify the mechanism of such pain. In the present case neuronal storage of glycolipid was confined to dorsal root ganglia neurones only. It is suggested that this may explain the shooting pain in Fabry's disease. In hereditary sensory radicular neuropathy, familial dysautonomia, and tabes dorsalis, changes in dorsal root ganglia cells cause similar clinical signs and thus it may be concluded that shooting pains in Fabry's disease may be caused by damage to dorsal root ganglia neurones.

Received for publication 28 June 1982.
Accepted for publication 10 December 1982.

Fabry's disease is an X linked recessive, glycolipid storage disease, affecting endothelium, myocardium, fibroblasts, epithelial cells of the glomerulus, smooth muscle, cornea, glial cells, and neurones. Storage of di- and triglycosylceramide in the affected tissues is believed to be caused by α -galactosidase A deficiency.¹

Early in the course of the disease the young patient suffers from bouts of severe, spontaneous shooting pain, usually in the distal part of his extremities but sometimes involving teeth, jaws, and abdomen. This characteristic symptom lacks a solid neuropathological correlation. Two possible theories have been advanced, that the pain is caused by damaged peripheral nerve endings or by depletion of small myelinated fibres in peripheral nerves.² The present report describes a patient with Fabry's disease in whom, in addition to the usual visceral