

Citrullinemia and Transposition of the Great Arteries

S. Udani
J. Dalal

Citrullinemia is an autosomal recessive disorder(1) whereas transposition of the great arteries (TGA) is known to have a multifactorial inheritance(2). We report a newborn seen immediately after birth with a combination of these two rare disorders.

Case Report

The baby was born at term by an elective cesarean section with Apgar scores of 8 at one minute and 9 at five minutes after birth and a weight of 2700 g. The parents were first cousins and had a history of an abortion in the late second trimester and a death of a full term male child at the age of 5 days with convulsions and coma. This pregnancy was uneventful with no history of diabetes, use of amphetamines, trimethadione or sex hormones which are associated with TGA(2).

She was seen at the age of 28 h for cyanosis treated as hypoglycemia. On examination the baby weighed 2700 g with a head circumference of 33.5 cm. She had no dysmorphic features. She was hypothermic,

lethargic and deeply cyanosed. The anterior fontanel was flat and the cry fairly good. There were no obvious congenital malformations. The heart rate was 110/min, regular, without gallop. The heart sounds were unremarkable and there was no murmur. The chest was clear with the liver palpable 1 cm below the costal margin.

Her investigations revealed the following in serum: Na 140 mEq/L, K 4.5 mEq/L, Ca 8.8 mg/dl, glucose 135 mg/dl, BUN 4 mg/dl, creatinine 1 mg/dl, Mg 2.3 mg/dl and SGOT/PT 72/24 units/dl. The arterial blood gas studies showed a pH 7.3, PaCO₂ 28 torr, PaO₂ 25 torr and BE 11. An X-ray of the chest showed a normal sized heart with unremarkable contour and pulmonary vasculature. Two-dimensional echo and Doppler studies revealed "d" transposition of the great vessels. A small patent foramen ovale was seen but no large ASD or VSD was present. Cardiac catheterization and angiography confirmed the diagnosis of complete transposition with no intracardiac defects. A balloon atrial septostomy was performed using a 5F Rashkind balloon catheter. Following septostomy the arterial oxygen saturation improved from 25 to 50 torr giving an increase in oxygen saturation from 50-90%(3). Her pH rose from 7.3 to 7.38. A repeat echocardiograph confirmed the creation of a large ASD.

The procedure was done without sedation or anesthesia and the child was noticed to be unusually quiet. The improvement in her oxygen saturation was not matched by an improvement in her general condition. Soon thereafter the child's condition worsened with deepening coma and bouts of convulsions. On the third Echocardiogram an ASD was seen with a good left to right shunt. The pulmonary valve was seen to have good flow through it.

From the Departments of Pediatrics and Cardiology, P.D. Hinduja National Hospital and Medical Research Centre, Mahim, Bombay.

Reprint requests: Dr. Soonu Udani, Consultant Pediatrician, P.D. Hinduja National Hospital and Medical Research Centre, Veer Savarkar Marg, Mahim, Bombay 400 016.

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Further investigations for coma and convulsions were conducted. The CSF was normal as was an ultrasound examination of the head. The serum calcium was 6.6 mg/dl and intravenous calcium was given. The blood ammonia was 560 mmol/L, (normal 50-80 mmol/L). In view of the hyperammonemia without significant acidosis, studies for the urea cycle disorders were undertaken. The plasma citrulline was 1.9 mmol/L (>1 mmol/L diagnostic of arginino succinic acid synthetase deficiency). Acylcarnitine was negative, arginine was low at 13.0 (Normal 50-120) nm/ml. Citrulline levels of the parents were both normal (<0.4 mmol/L).

An emergency double volume exchange transfusion was done after collecting samples of blood and urine for amino acidograms. The parents refused any peritoneal dialysis when the final diagnosis of TGA with citrullinemia due to arginino succinic acid synthetase deficiency was apparent.

Discussion

The urea cycle is the only known metabolic pathway for urea synthesis in man and is the major pathway of ammonia detoxification. Deficiency of the enzyme activities of this cycle is associated with hyperammonemia, intolerance to protein ingestion and mental retardation. The liver is the only organ that is quantitatively important in urea synthesis in spite of the presence of the complete urea cycle in human brain and kidney. The activity of argininosuccinic acid synthetase (ASAS) and argininosuccinase can be measured in cultured skin fibroblasts and amniotic fluid cells making prenatal diagnosis possible at a few centers in the world. There are five steps, each with a rate limiting enzyme, in the biosynthesis of urea.

Unexplained coma and/or convulsions should alert one to the possibility of an in-born error of metabolism. The absence of acidosis virtually rules out the organic acidurias. An elevated ammonia level will be seen in any of the Urea Cycle disorders. Only further tests for the accumulating precursor or an actual enzyme assay itself will pinpoint the defect. The causes of neonatal hyperammonemia without acidosis are (4): (1) Liver failure; (2) Urea Cycle Disorders: (i) Carbamyl phosphate synthetase (CPS) deficiency: Clinical presentation is similar but CPS deficiency is easily distinguished from the other urea cycle disorders by the absence of orotic acid in the urine; (ii) Ornithine transcarbamylase (OTC) deficiency: X-linked dominant transmission. There is complete absence of the enzyme in the hemizygous male and partial deficiency in the heterozygous female, where it may vary from 19 to 97% of normal. (iii) Citrullinemia (discussed below); and (iv) Argininosuccinic acidemia: Two syndromes described; the neonatal one is inherited by autosomal recessive transmission and has a poor prognosis. The infantile form is compatible with long survival; and (3) Transient hyperammonemia of the preterm has not been described in the full term baby.

ASAS deficiency was first discovered by McMurray *et al.* in 1962(5). Three types are known, neonatal, subacute and late onset (from Japan) which is different from all other urea cycle enzymopathies and has never been adequately explained. Citrullinemia as seen outside of Japan is inherited as an autosomal recessive trait. The structural gene for ASAS expression is carried on chromosome 9(1). The enzyme defect may demonstrate several different forms indicating genetic heterogeneity(6).

In deficiency of ASAS, the huge amounts of citrulline which accumulate may be toxic. Citrulline inhibits brain glucose utilization and lactate production *in vitro*. Ammonia elevation leads to stupor and coma and when it occurs in early life is likely to be more injurious, cerebral atrophy being a frequent finding on autopsy(7). Slow mental development may be the reaction of the growing brain to any toxic agent or injury.

Parents are clinically asymptomatic and may have normal plasma citrulline levels(1), as in our case. In our patient, the consanguinity and death of a sib in the neonatal period of similar symptoms indicate an autosomal recessive inheritance. Where the defect is partial, lifelong treatment with sodium benzoate (alternate pathway for ammonia utilization), arginine (the absent distal amino acid) supplements and a low protein diet (0.6 g/kg/day) may help physical and mental growth(8). Prenatal diagnosis of this condition is potentially possible since this enzyme has been demonstrated in normal amniotic fluid cells(9).

Visakorpi(10) reported a possible case of citrullinemia with cystinuria but there are no reports that have associated it with cardiac malformations. Our patient had a TGA, a condition that has an incidence of about 4.7% of all congenital heart disease seen in infancy(11). The exact incidence in the general population is very hard to determine. TGA is rarely associated with other syndromes and less than 7% have extracardiac malformations(11). TGA has been reported in Carpenter's syndrome and Klippel-Feil syndrome(2). In general, it appears to be by multifactorial inheritance resulting from an interaction of genetic and environmental factors(2). The genetic predisposition is presumed to be

polygenic, *i.e.*, the small additive effects of many genes.

A single locus or a small number of loci interacting with environmental influences may also be proposed. The gene for citrullinemia is on chromosome 9. It may be postulated that a neighboring or related locus could carry a gene that on mutation causes TGA similar to heart disease seen in chromosomal aberrations such as trisomy 21 and Turner's syndrome. Genetic counselling for such a family would then have to include separate risk counselling for congenital heart disease. TGA has already been described in association with an autosomal recessive disorder, Carpenter's syndrome(2). Here we describe it in association with ASAS deficiency or citrullinemia.

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REFERENCES

1. Walser M. Urea cycle disorders and other hyperammonemic syndromes. *In: The Metabolic Basis of Inherited Disease*, 5th edn. Eds Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS. Boston, Mc Graw Hill, 1983, pp 402.
2. Nora JJ, Nora AH. The evolution of specific genetic and environmental counselling in congenital heart disease. *Circulation* 1978, 47: 205-213.
3. Baker F, Baker L, Zoltun R, Zuberbuhler JR. Effectiveness of the Rashkind procedure in transposition of the great arteries in infants. *Circulation* 1971, 43: Supp I: I-1-6.
4. Volpe JJ. Hyperammonemia and other

disorders. *In: Neurology of the Newborn*, 2nd edn. Ed Volpe JJ. Philadelphia, WB Saunders Co. 1987, pp 421.

5. McMurray WC, Mohyuddin F, Rossiter RJ, *et al*. Citrullinemia. A new aminoacid disorder associated with mental retardation. *Lancet* 1962, 1: 138-142.
6. Kennaway NG, Harwood PJ, Ramberg DA, Koler RD, Buist NRM. Citrullinemia: enzymatic evidence for genetic heterogeneity. *Pediatr Res* 1975, 9: 554-558.
7. Shannon DC, Delong R, Bercu B, *et al*. Studies on the pathophysiology of encephalopathy in Reye's syndrome: hyperammonemia in Reye's syndrome. *Pediatrics* 1975, 56: 999-1004.
8. Msall M, Batshaw ML, Suss R. Neurologic outcome in children with inborn errors of urea synthesis: Outcome of urea-cycle enzymopathies. *New Engl J Med* 1984, 310: 1500-1502.
9. Roerdink FH, Gouw WLM. Citrullinemia: Report of a case with studies of antenatal diagnosis. *Pediatr Res* 1973, 7: 863-869.
10. Visakorpi JK. Citrullinemia. *Lancet* 1962, 1: 1357-1360.
11. Neches WH, Park SC, Etteedgui JA: Transposition of the great arteries. *In: The Science and Practice of Pediatric Cardiology*, Vol II. Eds Garson, Bricket & McNamara, Pennsylvania, Lea & Febiger. 1990, p 1174.

Cerebro Vascular Accident in Mitral Valve Prolapse

M.L. Kulkarni
A.C. Basavaraj
C. Sureshkumar
K. Farooq

Mitral valve prolapse (MVP) is a common clinical entity with a frequency in the

general population of 5-7%(1). The frequency in pediatric population is 1%(2). MVP is the most common cardiac abnormality observed echocardiographically in stable newborn girls(3).

The vast majority of patients with MVP have no serious complications. However, there are a few major complications, that may accompany MVP, they are: chest pain, progressive mitral regurgitation, infective endocarditis, thromboembolism, serious arrhythmias and sudden death(4).

Thromboembolism leading on to cerebrovascular accidents (CVA) is occasionally reported in adults(5). But its occurrence in pediatric age groups is exceedingly rare and no such cases have been reported in the literature, that too, from a clinically silent MVP. We report such a case.

Case Report

A 10-year-old girl was admitted with history of sudden onset of weakness in right upper and lower limbs associated with inability to talk, 6 months prior to admission.

Physical examination revealed that her anthropometric measurements were normal for her age. Her pulse was 80 beats per minute and regular, BP was 100/70 mm of Hg. All her peripheral arterial pulsations were well felt. She had no neurocutaneous markers or cutaneous changes seen in collagen vascular disorders. Central nervous system examination revealed that she had expressive aphasia, right sided upper

From the Department of Pediatrics, JJM Medical College, Davangere 577 004, Karnataka
Reprint requests: Prof. M.L. Kulkarni, 2373, M.C.C. 'A' Block, Davangere 577 004, Karnataka.

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