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Systemic hypertension in two patients with ASL deficiency: A result of nitric oxide deficiency?

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Abstract

Argininosuccinic aciduria (ASA) is an inborn error of ureagenesis which if untreated leads to hyperammonemia, accumulation of argininosuccinic acid and arginine depletion. The presence of high blood pressure in patients with ASA has been reported so far as transient in one newborn. We describe the first two patients, one child and one young adult, with ASA and persistent systemic hypertension. Extensive evaluation of both patients excluded secondary causes of systemic hypertension. The intriguing link between nitric oxide (NO) production and hypertension lead us to hypothesize that endogenous synthesized arginine deficiency caused by ASL deficiency is responsible for the increased blood pressure.

Keywords

Argininosuccinic aciduria; urea cycle disorders; Nitric oxide; hypertension

Introduction

Argininosuccinic aciduria (ASA) (MIM 207900) is a rare, autosomal recessive defect of urea cycle resulting from L-argininosuccinate lyase (ASL; EC 4.3.2.1) deficiency. The reported incidence of this disease is about one in 70,000 live births in the United States (1), and thus, it is the second most common heritable disorder of the urea cycle. Patients with this disorder typically develop in the newborn period or during infancy vomiting, lethargy, developmental delay, and hyperammonemia. The biochemical hallmarks of this disease are elevations of the amino acids argininosuccinic acid and citrulline and low levels of plasma L-arginine. Current treatment consists of a low-protein diet and L-arginine supplementation (2). However, despite treatment, patients often exhibit intellectual impairment and delayed motor skills. These consequences are mainly due to hyperammonemia, although it has been suggested that at least some of them might be due to deficiency of urea cycle intermediates (3). Hypertension which resolved with intravenous infusion of L-arginine has been reported in a newborn with ASA (4). The effect of L-arginine on blood pressure was further suggested by a second infant, reported by the same authors, who was administered intravenously with L-arginine for pituitary

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function evaluation and developed a drop in blood pressure responsive to discontinuation of L-arginine infusion (4). Indeed, it has been shown in normal children that L-arginine infused systemically can lower blood pressure (5). It is logical to hypothesize that ASL deficiency with a consequent intracellular arginine deficiency leads to nitric oxide (NO) deficiency. Here we report two patients of 19 and 9 years of age, with early- and late-onset ASA respectively, affected with systemic hypertension. The patients we described here further suggest the beneficial effects of NO donor and urea cycle intermediates on blood pressure in ASL deficiency.

Case reports

In the last 2 years 47 patients with a urea cycle disorders have been regularly seen for follow-up visits in the Metabolic Clinic of Baylor College of Medicine at Texas Children's Hospital, Houston, TX. Of these 47 patients, 25 were affected with ornithine transcarbamylase (OTC) deficiency, 2 with carbamyl phosphate synthetase (CPS) deficiency, 5 with citrullinemia, 7 with ASA, and 8 with argininemia.

Among the OTC deficiency case, only one 68 year-old woman was found to have mild increase in blood pressure. None of the patients with CPS deficiency, citrullinemia, and argininemia was found to have hypertension. Two out of the 7 patients with ASA were found to have increased systemic blood pressure and they are discussed in details below.

Case 1

This patient is now a 19 years old Caucasian female who was diagnosed with ASA few days after birth because of lethargy, poor feeding, and seizures which rapidly evolved into a comatose state. The patient presented with hyperammonemia (NH_4^+ 830 $\mu\text{mol/L}$) and the typical amino acid profile of ASA. The diagnosis was further confirmed by enzyme assay on patient's fibroblasts and red blood cells. The patient was treated with protein restriction diet, and L-arginine. However, she developed seizures and several episodes of hyperammonemia during intercurrent illnesses which progressed into a coma on two occasions. The patient's growth was insufficient ranging from values below the 5th percentile. Her weight was between the 10th and 25th percentile. Her psychomotor development was delayed and the patient continues to display mental retardation. At 17 years of age, she was first noted to have high blood pressure values, with systolic values ranging from 130 to 165 mm Hg and diastolic pressure ranging from 80 to 100 mm Hg. Hypertension was confirmed by 24 hr ambulatory blood pressure monitoring (ABPM). Serum electrolytes, creatinine, BUN and urinalysis were normal. Plasma renin and aldosterone, renal ultrasound and echocardiogram were all normal. Blood pressure was controlled with nifedipine treatment. The patient's family history is significant for the occurrence of systemic hypertension, in the grandmother and for gestational hypertension in the mother.

Case 2

This male patient is the first child of healthy Caucasian parents. Family history shows no record of premature infant deaths, kidney disease, hypertension, or other known genetic disorders. The patient was born at term after an uncomplicated pregnancy. His neonatal period was uneventful. At the age of 3 years he developed absence seizures, vomiting, failure to thrive, and feeding problems and was diagnosed with late-onset ASL deficiency on the basis of typical serum amino acids profile. He also had sparse, brittle hair. In vivo stable isotope nitrogen flux study (6) confirmed the biochemical defect and he was also shown to have 14% of residual enzymatic activity. The patient has been well controlled on low protein diet and L-arginine and had never experienced hyperammonemic crises. His growth has been in the 50th-75th percentile for stature, between 75th-90th percentile for weight and in the 50th-95th percentile range for

head circumference. No hepatomegaly was present. The patient presented a delay in the acquisition of normal psychomotor development milestones. His IQ level, evaluated at 6 years of age, was 55. Persistent high blood pressure was first evidenced at 6 years of age. The blood pressure range was between 130 and 165 mm Hg for systolic and 80-90 mm Hg for diastolic pressure, both over 95th percentile (7). The child did not complain of shortness of breath, palpitations, headache or any symptoms related to high blood pressure. A 24 hours ABPM confirmed the presence of hypertension (8). ABPM was repeated several times over the next few months and always showed similar pattern of blood pressure, with elevation of awake and asleep blood pressure levels. Serum electrolytes, creatinine, BUN and urinalysis were always normal. Renal ultrasound with Doppler flow revealed normal kidneys and absence of signs of renal artery stenosis. An echocardiogram did not reveal any cardiac abnormalities. Plasma renin and aldosterone were not increased. 24 hours urinary catecholamines, urinary homovanillic and vanillylmandelic were all within normal range. In order to control the hypertension, the patient was started on sodium-restricted diet and nifedipine (0.3 mg/kg/day). However, his blood pressure continued to remain elevated until propranolol (1.2 mg/kg/day) was added. No evident correlation was found between serum L-arginine levels and blood pressure.

In both cases there was not a clear correlation between plasma concentrations of citrulline, arginine, and ornithine and levels of blood pressure. Moreover, the plasma concentrations of these amino acids did not differ between the two ASA patients with hypertension and the other five patients with normal blood pressure followed at our center.

Discussion

The presence of high blood pressure in patients with ASA can be anticipated based on pathophysiological speculations. L-Arginine production, which is dramatically reduced in ASA, is an important vasodilator and its action is mediated through NO synthesized by endothelial cells from L-arginine (9). Several studies have shown that NO plays a crucial role in the pathogenesis of hypertension (10,11). However, so far only one patient, who developed transient hypertension in the newborn period resolving rapidly thereafter, has been reported (4). We describe the first two patients, one child and one young adult, with ASA and persistent systemic hypertension. The blood pressure in both patients was significantly elevated as confirmed by the ABPM, which is considered the most accurate tool for the diagnosis of hypertension in children (12) and the best predictor of complications (13). The blood pressure was constantly high throughout the day with few oscillations over the mean value in both patients.

In the few follow-up studies available on patients with ASA (3,14), high blood pressure has not been described as long term complication so far. The occurrence of hypertension in ASA may have been overlooked, although this is unlikely since blood pressure measurement is part of routine pediatric examination. It is possible that therapy with L-arginine may prevent the development of hypertension, although there have been no report of hypertension in poorly controlled patients and in both our cases we were not able to identify any correlation between the metabolic control, serum L-arginine and the severity of the hypertension. The blood pressure of our patients was constantly elevated with few oscillations within the normal range, as shown by the ABPM. We hypothesize that endogenously synthesized arginine plays an important role in blood pressure regulation and that compartmentalization of intracellular sources of arginine produced by ASL vs. extracellular sources of arginine (from the diet and from the kidney) may account for differences in contributions of NO production. Hence, supplementing with arginine may have a less optimal beneficial effect in this scenario.

We cannot rule out that the co-occurrence of systemic hypertension and ASA in these two patients is simply coincidental. Incidence of hypertension is not rare in childhood and it affects overall 1-3% of the pediatric population (15). However, the increased blood pressure in children is often secondary to some underlying cause and in both our patients no responsible cause was identified despite extensive diagnostic work-up. The intriguing link between NO production and ASL deficiency lead us to hypothesize a metabolic derangement as responsible of the increased blood pressure in our patients. Interestingly, we have generated a hypomorphic mouse model of *Asl* which survives beyond the newborn period and it also exhibits systemic hypertension (unpublished results, personal observation). Alterations in the L-arginine-NO pathway are well known causes of hypertension (16). The vascular endothelium converts L-arginine via NO synthase to L-citrulline and NO which, in turn, causes vasodilatation. Endothelial cells using component of urea cycle (AS synthase and ASL) can then synthesize endogenous L-arginine by recycling L-citrulline.

Links between urea cycle intermediates and hypertension have been identified in newborns with persistent pulmonary hypertension (17) and significantly low plasma concentrations of both L-arginine and NO metabolites have been found in patients with pulmonary hypertension secondary to cardiopulmonary bypass (18). This latter group of patients presents during the postoperative period significantly decrease in urea cycle intermediates, including L-arginine, leading to a decrease in NO which is likely to be responsible for pulmonary hypertension (18).

Patients with ASA may also suffer from progressive hepatic disease (19-21) without hypertension, which ultimately may evolve to cirrhosis. The pathogenic mechanism is unknown but, interestingly, NO has been associated also with pathogenesis of liver cirrhosis (22). Specifically, it has been proposed that reduced NO production may lead to impaired blood pressure regulation in the liver and this can result in hepatic fibrosis (22). It's intriguing that urea cycle intermediates have been related to hypertension restricted to pulmonary circulation (17) and perhaps liver circulation while in our two patients hypertension was systemic. These differences may suggest a different sensitivity, perhaps genetically established, of the different circulatory districts to NO.

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References

1. Levy, HL.; C, J.; Shih, VE. Newborn urine screening. Berlin: Springer-Verlag; 1980.
2. Brusilow, SW.; H, A. Urea cycle enzymes. New York: McGraw-Hill; 2001.
3. Widhalm K, Koch S, Scheibenreiter S, Knoll E, Colombo JP, Bachmann C, et al. Long-term follow-up of 12 patients with the late-onset variant of argininosuccinic acid lyase deficiency: no impairment of intellectual and psychomotor development during therapy. *Pediatrics* 1992;89(6 Pt 2):1182-4. [PubMed: 1594374]
4. Fakler CR, Kaftan HA, Nelin LD. Two cases suggesting a role for the L-arginine nitric oxide pathway in neonatal blood pressure regulation. *Acta Paediatr* 1995;84(4):460-2. [PubMed: 7795361]
5. Nelin LD, Hoffman GM. L-arginine infusion lowers blood pressure in children. *J Pediatr* 2001;139(5):747-9. [PubMed: 11713459]

6. Lee B, Yu H, Jahoor F, O'Brien W, Beaudet AL, Reeds P. In vivo urea cycle flux distinguishes and correlates with phenotypic severity in disorders of the urea cycle. *Proc Natl Acad Sci U S A* 2000;97(14):8021–6. [PubMed: 10869432]
7. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. *Pediatrics* 1996;98(4 Pt 1):649–58. [PubMed: 8885941]
8. O'Sullivan JJ, Derrick G, Griggs P, Foxall R, Aitkin M, Wren C. Ambulatory blood pressure in schoolchildren. *Arch Dis Child* 1999;80(6):529–32. [PubMed: 10332001]
9. Palmer RM, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature* 1988;333(6174):664–6. [PubMed: 3131684]
10. Haynes WG, Noon JP, Walker BR, Webb DJ. Inhibition of nitric oxide synthesis increases blood pressure in healthy humans. *J Hypertens* 1993;11(12):1375–80. [PubMed: 7510736]
11. Rees DD, Palmer RM, Moncada S. Role of endothelium-derived nitric oxide in the regulation of blood pressure. *Proc Natl Acad Sci U S A* 1989;86(9):3375–8. [PubMed: 2497467]
12. Sorof JM, Portman RJ. Ambulatory blood pressure measurements. *Curr Opin Pediatr* 2001;13(2):133–7. [PubMed: 11317054]
13. Belsha CW, Wells TG, McNiece KL, Seib PM, Plummer JK, Berry PL. Influence of diurnal blood pressure variations on target organ abnormalities in adolescents with mild essential hypertension. *Am J Hypertens* 1998;11(4 Pt 1):410–7. [PubMed: 9607378]
14. Parsons HG, Scott RB, Pinto A, Carter RJ, Snyder FF. Argininosuccinic aciduria: long-term treatment with arginine. *J Inher Metab Dis* 1987;10(2):152–61. [PubMed: 3116334]
15. Rames LK, Clarke WR, Connor WE, Reiter MA, Lauer RM. Normal blood pressure and the evaluation of sustained blood pressure elevation in childhood: the Muscatine study. *Pediatrics* 1978;61(2):245–51. [PubMed: 634679]
16. Chen PY, Sanders PW. L-arginine abrogates salt-sensitive hypertension in Dahl/Rapp rats. *J Clin Invest* 1991;88(5):1559–67. [PubMed: 1658045]
17. Pearson DL, Dawling S, Walsh WF, Haines JL, Christman BW, Bazyk A, et al. Neonatal pulmonary hypertension--urea-cycle intermediates, nitric oxide production, and carbamoyl-phosphate synthetase function. *N Engl J Med* 2001;344(24):1832–8. [PubMed: 11407344]
18. Barr FE, Beverley H, VanHook K, Cermak E, Christian K, Drinkwater D, et al. Effect of cardiopulmonary bypass on urea cycle intermediates and nitric oxide levels after congenital heart surgery. *J Pediatr* 2003;142(1):26–30. [PubMed: 12520250]
19. Zimmermann A, Bachmann C, Baumgartner R. Severe liver fibrosis in argininosuccinic aciduria. *Arch Pathol Lab Med* 1986;110(2):136–40. [PubMed: 3753845]
20. Saudubray JM, Touati G, Delonlay P, Jouvett P, Narcy C, Laurent J, et al. Liver transplantation in urea cycle disorders. *Eur J Pediatr* 1999;158. S55–9.
21. Mori T, Nagai K, Mori M, Nagao M, Imamura M, Iijima M, et al. Progressive liver fibrosis in late-onset argininosuccinate lyase deficiency. *Pediatr Dev Pathol* 2002;5(6):597–601. [PubMed: 12370774]
22. Farzaneh-Far R, Moore K. Nitric oxide and the liver. *Liver* 2001;21(3):161–74. [PubMed: 11422779]

Abbreviations

ASA	Argininosuccinic aciduria
ASL	L-argininosuccinate lyase
NO	nitric oxide
ABPM	

ambulatory blood pressure monitoring

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