Transient hyperammonaemia in an adult German shepherd dog

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ABSTRACT

A 3-year-old male German shepherd dog was presented with severe generalised seizures. The dog was protein-intolerant and showed severe hyperammonaemia on ammonia stimulation. The hyperammonaemic state was present for at least 6 weeks and then spontaneously resolved. No obvious cause (liver disease, portocaval shunts, urea cycle enzyme deficiencies, drug therapy or urinary tract obstruction) could be identified. It is possible that this dog had a variation of transient hyperammonaemic syndrome, described in man and recently in a juvenile Irish wolfhound, that extended into adulthood.

Key words: canine, dog, hyperammonaemia, seizures.

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INTRODUCTION

Hyperammonaemia has been described with urea cycle disorders, hepatic insufficiency, congenital or acquired portocaval shunting, urinary tract obstruction, drug therapy (valproic acid, asparaginase, narcotics and ammonium salts), hyperalimentation, gastrointestinal haemorrhage and high-protein meals[10]. This article describes a case in a dog in which none of these causes could be identified.

CASE HISTORY

A 3-year old, intact, male German shepherd dog was admitted to the Onderstepoort Veterinary Academic Hospital (OVAH) with severe generalised seizures. There was no history of trauma or exposure to toxins and his vaccination status was current. Clinical and neurological examinations were within normal limits. The only abnormalities on haematology and serum biochemistry profile were a mild lymphopaenia, mild hyperalbuminaemia, elevated activity of alanine transaminase (ALT) and a low serum urea concentration (Table 1). No abnormalities were evident on urine, faecal or cerebrospinal fluid (CSF) analyses. Serum canine distemper and toxoplasmosis (IgM and IgG) titres were negative. The basal ammonia concentration was within normal limits, but on stimulation, severe hyperammonaemia developed (Table 2). The stimulation was performed by dosing 100 mg/kg of ammonium chloride per os and determining the plasma ammonia concentration after 30 minutes. Portocaval shunt or liver disease was suspected. Further tests were, however, declined by the owner and the dog was discharged on a low protein diet (Hills k/d prescription diet).

Seven weeks later, the dog was readmitted to the OVAH with multiple, severe generalised seizures after ingesting a high protein meal. Prior to that, the owners reported that he was normal. Clinical and neurological examinations, and basal ammonia level were normal, but again, on stimulation, severe hyperammonaemia developed (Table 2). Abdominal ultrasonography was within normal limits. On exploratory laparotomy there were no obvious visible shunts and macroscopically the liver appeared normal. Portal pressure was 11 cm of water (normal 8–12). A portogram study, performed by catheterising a mesenteric vein, was within normal limits. Histology of the liver could not demonstrate any lesions that could account for the severely elevated ammonia levels. To rule out a congenital urea cycle enzyme deficiency, serum and urine were submitted for a metabolic profile (amino and organic acid analyses, including asparagine, alanine, citrulline, lysine, tyrosine, serine and arginine). The metabolic profile showed normal amino and organic acid analyses and no orotic acid or ornithine could be demonstrated in the urine.

No specific diagnosis could be made and the dog was maintained on a low protein diet (Hills k/d prescription diet). No further seizures occurred over the following 8 months. He was then again presented to the OVAH with severe generalised seizures. Both the basal and stimulated ammonia concentrations were within normal limits. Phenobarbitone therapy was instituted at 1 mg/kg bid, which controlled the seizures. Two months later he was re-admitted to the OVAH with cluster seizures. The serum phenobarbitone level at this point was sub-therapeutic (10.4 µg/mℓ; normal 14–40). Increasing the phenobarbitone to therapeutic levels (21 µg/mℓ), as well as instituting potassium bromide therapy has resulted in control of the seizures. Approximately every 6–8 weeks, he has a mild, generalised seizure. Serum phenobarbitone levels have remained in the therapeutic range. Since the introduction of anticonvulsant therapy he is being fed a normal canine maintenance diet.

DISCUSSION

The liver is of utmost importance in the regulation of ammonia, with 80–90 % of ammonia delivered to the liver converted to urea via the Kreb-Henseleit urea cycle. The other 10–20 % is metabolised by the kidneys, heart, brain, skeletal muscle and intestines[4]. Glutamate and glutamine are closely linked with blood ammonia concentration and encephalopathic signs. Glutamate is the initial product derived from protein catabolism through transamination reaction with a α-ketoglutarate and other amino acids. Glutamine is the second major product of hepatic ammonia metabolism; and in this form, ammonia can be stored and transported throughout the body[4].

Hepatocellular function is heterogeneous, as the metabolic constitution of periportal hepatocytes is different from that of perivenous hepatocytes. Periportal hepatocytes have a large capacity for ammonia metabolism by regulating glutaminase, which controls the flux of

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Table 1: **Haematology and serum chemistry.**

Parameter	4 July 95	4 April 96	28 May 96	Normal
Haemoglobin	172	155	154	120–180 g/ℓ
Red cell count	8.00	7.25	7.33	5.5–8.5 × 10^{12}/ℓ
Packed cell volume	0.54	0.48	0.46	0.37–0.55 ℓ/ℓ
Mean cell volume	67	69	62.6	60–77 f/ℓ
Mean cell haemoglobin concentration	32	32	33.6	32–36 f/ℓ
Total white cell count	12.1	11.4	15.7	6–15 × 10^{10}/ℓ
Neutrophils	10.2	10.03	13.03	3.0–11.5 × 10^{9}/ℓ
Band cells	0.12	0	0	0–0.3 × 10^{9}/ℓ
Lymphocytes	0.73	0.57	1.057	1.0–4.8 × 10^{9}/ℓ
Monocytes	0.36	0.68	0.79	0.15–1.35 × 10^{9}/ℓ
Eosinophils	0.73	0.11	0.31	0.10–1.25 × 10^{9}/ℓ
Basophils	0	0	0	Rare
Thrombocytes	224	208	232	200–500 × 10^{9}/ℓ
Total serum proteins	71.4	71.4	76.8	53–75 g/ℓ
Albumin	42.5	33.2	35.7	25–35 g/ℓ
Globulin	28.9	38.2	41.1	20–37 g/ℓ
Alanine transminase (ALT)	55	38	22	<40 U/ℓ
Alkaline phosphatase (ALP)	57	100	101	<190 U/ℓ
Sodium	151	155	150	140–155 mmol/ℓ
Potassium	4.2	4.3	4.4	3.6–8.8 mmol/ℓ
Calcium	2.79	2.62	2.67	2.2–2.9 mmol/ℓ
Glucose	6.5	5.3	5.9	3.3–5.5 mmol/ℓ
Urea	3.1	1.7	4.8	3.6–8.8 mmol/ℓ
Creatinine	111	108	107	<133 μmol/ℓ

Table 2: **Plasma ammonia concentrations.**

	5 July 95	22 August 95	4 April 96	10 April 96	28 May 96	Normal
Basal	14.7	17.3	14.7	9.5	12.9	4–30 μmol/ℓ
Stimulation	123.4	375.4	24.2	16.4	24.2	4–30 μmol/ℓ

ammonia into the urea cycle. By contrast, perivenous hepatocytes have limited capacity but high affinity for ammonia metabolism via glutamine synthetase. They therefore scavenge ammonia that escapes from periportal cells by synthesising glutamine. When periportal hepatocytes become damaged, ammonia metabolism by the perivenous hepatocytes becomes overwhelmed, leading to encephalopathic signs. Given time, remaining hepatocytes can potentially re-establish the regulatory scheme[6]. It is possible that this dog initially had a severe acute hepatic insult that resulted in a hyperammonaemic state; this is unlikely, however, because there were no clinical signs prior to the seizures, ALT activity was only marginally elevated, and there was no evidence on liver biopsy of a prior insult to the liver.

The urea cycle is the only known metabolic pathway for urea synthesis and is the major pathway of ammonia detoxification. Deficiencies of the enzyme activities in the cycle are usually associated with hyperammonaemia, intolerance to protein ingestion and mental deficiency. Hyperammonaemia has also been found in several other familial diseases or apparent inborn errors of metabolism[8].

The biosynthesis of urea requires 5 steps, each of which necessitates a specific enzyme. Enzymes involved are carbamyl phosphate synthetase (CPS), ornithine carbamyl transferase (OCT), argininosuccinate synthetase (ASA), argininosuccinase, and arginase[8]. The following is a summary of urea cycle enzyme and related deficiencies[8]. CPS deficiency results in protein intolerance, hyperammonaemia and low urinary orotic acid. OCT deficiency results in severe hyperammonaemia and severely elevated orotic acid in the urine. ASA deficiency results in hyperammonaemia and marked accumulation of citrulline in the blood, CSF and urine. Argininosuccinase deficiency results in neonatal death, mental retardation, seizures, ataxia, hepatomegaly, accumulation of large amounts of argininosuccinic acid in the blood, urine and CSF, and is frequently associated with friable tuft hair known as trichorrhexis nodosa. Arginase deficiency is characterised by variable hyperammonaemia, mental retardation and marked elevation of arginine in the blood, urine, and CSF. Organic acidaemias can result in severe hyperammonaemia and are recognised by the accumulation of organic acids in the blood and urine. Hyperammonaemia is also associated with the syndrome of hyperornithinaemia, hyperammonaemia and homocitrullinuria. Protein intolerance has also been described with congenital lysine intolerance and hyperlysinaemia, both of which are characterised by reduced plasma concentrations of arginine, lysine and tyrosine with elevated alanine, citrulline and serine concentrations. There is also increased lysine excretion in the urine.

Low blood urea and post-prandial hyperammonaemia are often observed. The cerebroatrophic syndrome of Rett is associated with mental retardation and hyperammonaemia[8].

This dog showed initial protein intolerance, seizures and hyperammonaemia. Common causes for these signs were ruled out. All 3 of these findings have been associated with urea cycle enzyme deficiencies. Although the specific enzymes in this case were not quantified, no abnormalities were evident on the metabolic profile and the protein intolerance and the hyperammonaemia resolved. Urea cycle enzyme deficiencies result in either an increase or decrease in blood and/or urine orotic acid, citrulline, argininosuccic acid, and arginine and other amino and organic acids. Based on the findings of the metabolic profile, it is unlikely that a urea cycle enzyme deficiency was present in this case.

The only urea cycle enzyme deficiency reported in dogs has been argininosuccinate synthetase deficiency[9]. One case described in a 4-month-old male golden retriever, and the second case in a 4-year-old male beagle. Although liver enzyme activity was low in both cases, no portal contrast studies were conducted and it is thus possible that both these dogs had portocaval shunts that contributed to the clinical signs.

Ammonia is generated by amino-acids obtained from the diet, from catabolism of glutamine by enterocytes, or from peripheral tissues such as skeletal muscle, the latter occurring with vigorous exercise[5]. Seizure activity in this dog could have resulted in increased production of ammonia, but this was unlikely because ammonia levels were determined 12–24 hours after the seizures were controlled and hyperammonaemia developed only on stimulation. Prior to the seizures, the dog was fed a normal canine adult maintenance diet.

The initial hyperammonaemic state that caused the seizures could have resulted in post-metabolic acquired epilepsy[3]. Since the patient was a German shepherd dog, it is also possible that true or idiopathic epilepsy was present[3]. The initial management with a low protein diet was adequate to control the seizures, and in fact re-exposure to a high protein diet resulted in seizures. Once the dog became normoammonaemic, a low protein diet did not control the seizures. Control of seizures with phenobarbitone, especially once the levels were therapeutic, favours a diagnosis of true epilepsy or post-metabolic acquired epilepsy.

The persistent lymphopaenia was attributed to a stress response and the elevated ALT as a result of possible hypoxia following a seizure. The was also initially a state of subclinical dehydration (hyperalbuminaemia). Both the hyperalbuminaemia and the elevated ALT resolved.

Transient hyperammonaemia has been described in pre-term human infants[1,2], and recently in Irish wolfhounds[7]. In man, there are 3 forms of hyperammonaemia affecting premature infants: asymptomatic transient hyperammonaemia, symptomatic transient hyperammonaemia; and hyperammonaemia due to a urea cycle enzyme deficiency[2]. The asymptomatic transient hyperammonaemia is what probably occurred in the wolfhound. It is possible that the German shepherd dog described in this report had a variation of the symptomatic transient hyperammonaemia syndrome, described in pre-term infants, that extended into adulthood. Why the condition remained clinically silent until 3 years of age is uncertain but it is possible that it was initially genuinely clinically silent, or that the seizures were missed by the owners either because they were not present or because the seizures were mild generalised or partial and thus overlooked when they occurred. Another possibility is that the problem only developed at 3 years of age.

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