Amino Acids (2005) 28: 51–56
DOI 10.1007/s00726-004-0149-6

Amino Acids
Printed in Austria

Infantile dilated cardiomyopathy in Portuguese water dogs: Correlation of the autosomal recessive trait with low plasma taurine at infancy

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Received August 19, 2004
Accepted October 26, 2004
Published online December 22, 2004;

Summary. Infantile dilated cardiomyopathy (IDCM) in Portuguese water dogs (PWD) involves an autosomal recessive trait. Based on our previous studies we have tested the hypothesis that this disorder may be correlated with taurine deficiency. The plasma taurine levels of 249 puppies from 36 litters obtained from breeders at six and nine weeks of age, an early stage when usually the clinical symptoms are not manifested, were analyzed. Additional samples were collected from sixteen puppies that we raised from four litters. These litters were born to a dam that had low plasma taurine as a puppy and two known carrier sires. From the random samples obtained from the breeders, forty-eight pups from fourteen litters and twenty-nine pups from seven litters had low plasma taurine at least at one and at two time points, respectively. Also several puppies showing low plasma taurine died due to IDCM. Furthermore, from the sixteen pups we raised, fifteen had at least low taurine level at one and seven had at two time points. Considered together, these results strongly support the view that IDCM in PWD is associated with abnormal taurine metabolism that leads to low plasma taurine at early stages before the clinical symptoms appear.

Keywords: Taurine deficiency – Canine infantile dilated cardiomyopathy – Low plasma taurine – Autosomal recessive trait

Introduction

Taurine (β-aminoethansulfonic acid) is a ubiquitous sulfur-containing amino acid derived from methionine. It is present in abundant quantities in mammalian plasma and tissues. To date it has not been reported to be incorporated in proteins. It is slowly metabolized in mammals. Taurine is synthesized in various cell types but liver is the major site of synthesis. It is secreted in the bile and urine and reabsorbed in the intestine and kidney (Huxtable, 1993). In mammals numerous factors may influence the amount of plasma taurine. They include dietary intake, endogenous synthesis as well as body requirements. Also there are species and age differences that may influence the levels of plasma taurine (Chapman et al., 1993).

Taurine is believed to confer pleiotrophic effects in numerous cellular processes. These include: development of the nervous system, neuromodulation, osmoregulation, plasmalemmal stabilization, myocardial function, regulation of calcium fluxes, and cell proliferation (Huxtable, 1993; Chapman et al., 1993). However, the mechanisms by which taurine affects these diverse physiological processes remain to be understood.

Dilated cardiomyopathy (DCM), a lethal disease characterized by dilation and systolic dysfunction of the heart is relatively common in humans and other mammals (Schonberger and Seidman, 2001; Towbin and Bowles, 2002). The etiologies of DCM are diverse and it is currently believed that many of these are associated with infections, autoimmune, nutritional, or metabolic disorders (Dec and Fuster, 1994). However, some genetic factors are also believed to be involved in the pathogenesis of idiopathic DCM (Tobin and Bowles, 2002; Olson and Keating, 1997). Recently an inherited infantile dilated cardiomyopathy (IDCM) was reported in Portuguese Water dogs (PWD) by us and others (Alroy et al., 2000; Dambach et al., 1999). It is a breed of dogs used by Portuguese fisherman for centuries and was traditionally fed with a diet of fish (Molinari, 1988). Our studies of IDCM in PWD have shown that this disorder

is transmitted as an autosomal recessive trait. We have also shown that in several affected pups with IDCM the plasma taurine level was significantly reduced, and the ultra structural changes were similar to those seen in myocardium of taurine deficient rats (Lake, 1993). Furthermore, the clinical and echocardiographic manifestations of IDCM were reversed following oral taurine supplementation (Alroy et al., 2000). An association between taurine deficiency and DCM has been previously reported in cats (Pions et al., 1987) and fox (Moise et al., 1991). We suggested that the autosomal recessive trait responsible for IDCM in PWD involves an impaired metabolism of taurine, probably affecting some rate-limiting step(s) in taurine biosynthesis and resulting in low taurine plasma level (Alroy et al., 2000).

In this report using a large representative number of samples from PWD pups of multiple litters we have analyzed the plasma taurine levels at six and nine weeks of age, a very early stage. Our results support the hypothesis that a low plasma taurine level is associated with IDCM in affected PWD pups. The significance of these results in relation to a possible role of taurine in myocardial contractility in normal and IDCM conditions is discussed.

Materials and methods

The study includes 249 puppies obtained from 36 litters of PWD. The litters varied in size from three to eleven puppies per litter. Samples of venous blood, were collected in EDTA containing tubes by the breeders at 6 weeks and from 230 pups at nine weeks of age, and the plasma was separated. In addition, we obtained plasma from thirty-four dams at six weeks postpartum. Information about the diet of the dams and puppies obtained from the majority of the litters and provided by the breeders indicated that the diet was quite diverse and contained meat supplement. We also collected blood at six and nine weeks from sixteen puppies that we raised from four litters selectively bred using two known carrier sires and a dam that as a puppy (number 18) had low plasma taurine and a progressive decrease in fractional shortening which was reversed following dietary taurine supplementation (Alroy et al., 2000). The puppies were fed a commercial diet, Natural Choice lamb and rice puppy food (Nutro, City of Industry, CA), and had moderate physical activity.

The chilled plasma samples were delivered overnight to the amino-acid Laboratory at the Floating Hospital, New England Medical Center in Boston. The plasma samples were diluted at 1:1 ratio with 3% sulfosalicylic acid, mixed, spun for twenty minutes at 2500 rpm, and the supernatant was removed. The samples were filtered and analyzed by HPLC using a Beckman 6300 analyzer. The intensity of the color developed after treatment with ninhydrin is estimated colorimetrically from the area under the peak scanned by a computer. The mean and standard deviation for the samples from the total number of puppies as well as those for each litter were calculated.

Results

To test the postulate that a low plasma taurine level in IDCM affected PWD pups is correlated with the autosomal recessive trait involving this disorder, it is important to study plasma samples from a large number of puppies from multiple litters. Two time points, at six and nine weeks age, an early stage where clinical symptoms of DCM, as shown by echocardiography are not usually observed, were used by the breeders for collecting the blood samples. The plasma taurine levels of 249 puppies obtained from 36 litters at six weeks of age and from 230 puppies at nine weeks of age as well as their mothers are shown in Table 1. The mean plasma taurine of 249 puppies, obtained from 36 litters, at six weeks of age was 96 μmol/L, the standard deviation was 68, and the range was 347 to 10 μmol/L. At nine weeks of age the mean plasma taurine of the 230 puppies was 95 μmol/L, the standard deviation was 55, and the range was 312 to 6 μmol/L. The mean plasma taurine of the mothers from multiple litters was 115, the standard deviation was 46, and the range was 232 to 12 μmol/l. It appears that the mean plasma taurine values for all of the puppies randomly used in this study did not show significant changes at six and nine weeks. The mean plasma taurine level of the mothers in the PWD breeds is somewhat higher than that reported previously for normal adult dogs, 63 μmol/L and ranging from 224 to 44 μmol/L (Kramer et al., 1995).

For comparative analysis of the plasma taurine levels in normal and IDCM affected pups from the same individual litter, taurine values lower than one standard deviation below the mean was considered as low. Table 2 shows a selective subset of data such as the number of pups in different litters with low plasma taurine, and their plasma taurine levels at six and nine weeks (for details see also Tables 1, 2 and text). Thirty four pups from eleven litters showed low plasma taurine levels at least at one time point. Furthermore, thirteen pups from four different litters had low taurine levels at two time points. At six weeks, plasma taurine level of twenty-one puppies from seven different litters was less than one standard deviation below the mean i.e., 28 μmol/L. At nine weeks twenty-four puppies from nine different litters had plasma taurine level that was less than one standard deviation below the mean, i.e., 40 μmol/L. In litter 4 all nine puppies had low taurine levels, i.e., one standard deviation below the mean, both at six and nine weeks of age. At six weeks the mean level for this litter was 18 ± 6 μmol/L and at nine weeks it was 8 ± 2 μmol/L. In addition, four puppies from three different litters, two from litter 11, one each from litter 15 and litter 26, had low levels of taurine both at six and nine weeks of age. It

Table 1. Plasma taurine levels (μmol/L) of PWD puppies and their mothers in multiple litters obtained randomly from breeders[a]

Litter number	Number of puppies in litter	Plasma taurine at 6 weeks		Plasma taurine at 9 weeks		Mother's plasma taurine at 6 weeks
		Mean ± SD	Range	Mean ± SD	Range	
1	6	77 ± 15	58–101	NA		105
2	9	85 ± 14	62–104	120 ± 26	78–137	109
3	11	60 ± 16	36–89	97 ± 36	37–173	148
4	9	18 ± 6	10–26	8 ± 2	6–11	70
5	5	100 ± 16	115–80	78 ± 10	70–93	141
6	5	41 ± 13	60–29	21 ± 4	15–25	68
7	6	121 ± 24	90–160	106 ± 10	92–120	55
8	5	102 ± 28	54–125	97 ± 17	68–110	131
9	5	113 ± 14	91–127	54 ± 23	26–74	171
10	10	60 ± 28	26–120	83 ± 31	41–123	147
11	9*	26 ± 7	18–35	43 ± 8	29–54	15
12	5	63 ± 10	49–74	94 ± 15	78–115	129
13	6	214 ± 75	116–308	106 ± 18	82–134	116
14	7	73 ± 31	45–106	103 ± 10	92–117	69
15	10	49 ± 41	21–157	65 ± 29	31–113	84
16	10	110 ± 40	78–217	90 ± 22	66–140	115
17	11**	42 ± 13	25–75	98 ± 22	70–145	115
18	9	72 ± 21	47–108	48 ± 12	29–62	72
19	3	153 ± 19	140–75	282 ± 34	243–307	132
20	3	182 ± 52	135–283	246 ± 58	205–312	89
21	6	223 ± 36	180–261	136 ± 28	111–181	125
22	9	59 ± 15	38–89	82 ± 19	53–104	NA
23	9	118 ± 43	77–156	65 ± 13	46–87	108
24	10	194 ± 56	95–253	121 ± 19	97–146	NA
25	7	114 ± 19	86–253	NA		109
26	6	62 ± 61	21–185	53 ± 16	26–73	61
27	8	49 ± 7	39–58	84 ± 26	52–129	NA
28	9	308 ± 40	245–346	217 ± 48	126–252	96
29	4	163 ± 58	100–241	147 ± 37	100–180	169
30	4	158 ± 27	138–195	145 ± 32	124–193	125
31	3	120 ± 7	114–127	NA		165
32	9	95 ± 20	62–123	135 ± 46	84–211	232
33	9	41 ± 12	30–69	50 ± 16	30–76	12
34	5	38 ± 12	22–53	59 ± 23	36–96	105
35	5	81 ± 16	70–108	132 ± 11	113–144	101
36	5	188 ± 35	136–225	173 ± 56	115–240	155

[a] For details see also text

NA, not available

* In litter 11 three pups died or were euthanized with IDCM

** In litter 17 one pup died with IDCM

should be noted that in litter 11 three out of nine pups and in litter 17 one pup who had low plasma taurine at six weeks of age, died or were euthanized due to IDCM (Tables 1 and 2). Furthermore, two dams (litters 11 and 33), had strikingly low level of plasma taurine. In these litters the plasma taurine of all pups was relatively low, and in one of these litters three puppies died or were euthanized due to IDCM (Table 1).

With regard to the sixteen puppies from four litters selectively bred using known carriers (see also Methods and materials), the mean plasma taurine at six weeks was 28 μmol/L, the standard deviation was 20, and the range was 66 to 4 μmol/L. The mean plasma taurine at nine weeks of fifteen of these puppies was 13 μmol/L, the standard deviation was 76, and the range was 29 to 4 μmol/L. It should be noted that all of the sixteen puppies had low plasma taurine level at least at one time point and seven had at two time points (Table 3). This high incidence of low plasma taurine observed in puppies born to known carries, is in contrast to the results obtained with random samples from multiple litters supplied by breeders (Tables 1 and 2).

Table 2. Low plasma taurine levels (μmol/L) of PWD puppies from multiple litters[a]

Litter	Number of pups in litter	Number of pups with low taurine	Mean of low plasma taurine levels in pups at	
			6 weeks	9 weeks
4	9	9	18	8
6	5	5	40[d]	21
9	5	2	124[e]	28
10	10	1	26	56[d]
11	9	5[b]	21	31
15	10	3	26	31
17	11	1[c]	25	81[d]
18	9	2	57[d]	30
26	6	1	21	26
33	9	3	24	34
34	5	2	22	36

[a] This table shows a subset of data selected for low plasma taurine levels from the samples shown in Table 1. For details see also text and Table 1
[b] In litter 11 three pups died or were euthanized with IDCM
[c] In litter 17 one pup died with IDCM
[d] The plasma taurine in these puppies was below the mean
[e] The plasma taurine in these puppies were just above the mean

Table 3. Plasma taurine levels (μmol/L) of puppies from litters selectively bred with known carriers[a]

Litter number	Sex of puppies	Taurine level at 6 weeks	Taurine level at 9 weeks
Litter 1			
	F	66	10
	F	37	12
	F	30	18
	F	31	15
	M	48	29
Litter 2			
	M	47	18
	F	16	9
	M	13	14
	F	14	10
	F	66	13
	F	9	7
Litter 3			
	M	10	6
	F	6	9
	F	4	NA
	M	27	4
Litter 4			
	F	18	14

[a] For details see also text
NA, not available

Discussion

It is currently believed that both cardiac and skeletal muscle have a slow rate of taurine turnover (Matsubara et al., 1985), and the concentration of plasma taurine appears to be a valuable indicator of skeletal muscle taurine concentrations (Pacioretty et al., 2001). In a previous study (Alroy et al., 2000) we have shown that in a litter of nine pups, eight puppies that were affected with IDCM showed very low plasma taurine concentration. Also, oral supplementation of taurine for two months starting at 106 days, when clinical symptoms were clearly manifested, increased plasma and whole blood taurine levels and improved cardiac function (Alroy et al., 2000). However, it should be noted that in the above-mentioned studies only a limited number of puppies available from a single litter were used.

Our results using a number of puppies from multiple litters demonstrate that a significant number of puppies had low plasma taurine levels at early stage e.g. at six or nine weeks or both (see Tables 1, 2 and 3). Furthermore, the observed decrease in plasma taurine level ranged from one to two standard deviations below the mean. Since the samples were obtained randomly, the variation in plasma taurine levels of puppies from the same or different litters may in part due to multiple contributing parameters such as the time interval between the blood collection and the last meal of the puppy, the content of taurine in the diet as well as the physical activity. It was observed that several puppies that had low plasma taurine level as early as six weeks (for example three in litter 11 and one in litter 17) died or were euthanized due to IDCM. With regard to the plasma taurine level of the mothers, two dams (litter 11 and 33) that had very low level, the mean plasma taurine of all of the puppies in their litter was strikingly low. Also three puppies in one of these litters died or were euthanized due to IDCM. Finally, the sixteen puppies selectively bred using known carriers and maintained with moderate degree of physical activity, and a known diet, showed a much higher incidence of low plasma taurine levels than the random samples from multiple litters supplied by the breeders (Results and Table 3).

Taurine is considered to be an essential nutrient for some mammalian species e.g. cats, foxes and possibly primates, including humans (Hayes et al., 1975; Geggel et al., 1985; Hayes, 1985). In newborn animals the amount of taurine intake from mother's milk varies during lactation and is dependent on maternal diet (Kim et al., 1996). Also, the synthesis of taurine is likely to be more restricted in neonates (Sturman and Hayes, 1980; Sturman, 1993). There are species and age differences that may influence the levels of plasma taurine in mammals. In general, smaller species have higher levels of plasma taurine than larger species, and neonates have higher levels than adults (Chapman et al., 1993). In cat and fox the

endogenous synthesis of taurine is absent or weak. In both species, whose natural diet is meat, lack or deficiency of dietary taurine leads to cardiomyopathy (Pion et al., 1987; Moise et al., 1991).

With regard to the role of taurine in normal myocardial function it should be noted that the concentration of taurine in the myocardium is high and accounts for up to 60% of the free amino acid pool (Huxtable, 1993). In contrast, the concentration of taurine in the plasma is lower and this creates a large taurine gradient across the sarcolemma (Suleiman et al., 1997). It is currently believed that taurine levels regulate the shape and size of neonatal cardiomyocytes (Schaffer et al., 1998). Taurine influences ion transport through various channels in cardiomyocytes. It has been suggested that taurine potentiates Ca^{2+} uptake by the sarcoplasmic reticulum, increases the sensitivity of the myofilaments to Ca^{2+} (Steele et al., 1990), and affects the long lasting (i.e., L-type) voltage-dependent Ca^{2+} channel (Liu et al., 1998). It was proposed that taurine indirectly increases Ca^{2+} influx by inducing Ca^{2+} via the Na^{+}–Ca^{2+} exchanger (Bkaily et al., 1998). In addition, taurine influences the action potential duration in cardiomyocytes, and modulates the rapid K^{+} current (I_{kr}) but not the slow K^{+} current (I_{ks}) (Satoh, 1999). Some or all of these features may play a critical role in the cardiac function of young small sized animals.

Two novel taurine – containing modified uridines has been recently identified as constituents of human and bovine mitochondrial tRNAs (Suzuki et al., 2002). These authors have also shown that in mutant mitochondrial tRNAs obtained from cells of human patients with mitochondrial encephalomyopathic diseases, the enzymatic modification of the taurine containing uridines is lacking or severely impaired. In another recent report it has been suggested that taurine deficiency leads to DNA damage that results in the arrest of cardiomyocyte cell cycle and growth (Golubnitschaja et al., 2003). The involvement of taurine in mitochondrial tRNA metabolism and cardiomyocyte cell cycle has been implicated as possible underlying factors in the pathogenesis of DCM. However, it should also be noted that DCM in mammals are caused by diverse etiologies.

Considered together with our earlier work (Alroy et al., 2000) we propose the following hypothesis: in PWD there is an autosomal recessive trait that results in low levels of plasma taurine. It is manifested in the first few months when the heart rate of taurine in affected puppies is normally faster than adult PWD, and the need for plasma and tissue levels is higher than those in adult PWD. This view is supported by reports in the literature showing that the heart rate of neonate is higher than adults (Detweiler, 1993) and changes in plasma taurine levels occur after endurance events (Ward et al., 1999; Cuisiner et al., 2002). Therefore, in affected pups due to a low level of taurine in plasma and cardiomyocytes, a sudden demand for increased cardiac output may result in acute DCM and sudden death. The absence of myocardial cell injury, death and fibrosis in IDCM affected PWD pups (Alroy et al., 2000) also supports this hypothesis.

Routine estimations of plasma taurine levels at early stages in PWD puppies may also serve as a quick, convenient and inexpensive monitoring approach for the selection of puppies to be further examined by clinical evaluations. Also, this approach has the potential for removing the carriers from the breeding program. In addition, our results have relevance to the identification of the candidate gene(s) affected by the autosomal recessive trait involved in this disorder. We speculate that IDCM in PWD may involve a decreased activity of some rate limiting enzymes in the hepatic cysteine sulfinic decarboxylase pathway for taurine biosynthesis.

Acknowledgements

The authors thank Ms. L.D. Cowell and Ms. B. Brewer, for their technical, and Mrs. B. Elkevich and Mrs. J. Penn for their assistance in the preparation of the manuscript. These studies were supported by funds from the Nutmeg Portuguese Water Dog Club, from the Canine Health Foundation and Tufts University School of Veterinary Medicine, and contributions by Mrs. J.L. Chiara and Mrs. K. Miller-Stebbing.

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