

# The potential value of red cell transketolase in the metabolic evaluation of disease

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Transketolase is a thiamine pyrophosphate dependent enzyme, which occurs twice in the hexose monophosphate shunt.<sup>1</sup> A number of investigators have used it in assessing intracellular cofactor deficiency, since it occurs in red cells, which are easily obtainable for testing.<sup>2-4</sup> Two aspects must be considered in the use of this enzyme as a clinical tool. In the first part of the assay, activity is measured by determining the amount of sedoheptulose-7-phosphate produced per unit of time. By adding thiamine pyrophosphate, the speed of production is measured again. Two values are reported: the initial measured transketolase activity (TKA) and thiamine pyrophosphate percentage uptake (TPP%), sometimes referred to as the thiamine pyrophosphate effect (TPPE).<sup>5</sup> Although we have found this enzyme assay to be abnormal in a number of clinical situations for reasons incompletely understood, we have chosen the cases of four children to illustrate an innovative approach that applies a biochemical principle in attempting to study a disease whose clinical expression may reflect defective energy metabolism. The cases chosen have a neurologic background, but do not represent a homogenous disease entity in the traditional manner. All four children were treated with large doses of thiamine hydrochloride; this therapy was based

on the results of TKA and TPPE assays, one or other of which was shown to revert to normal after therapy and correlated well with the individual clinical response as well as changes in creatine and creatinine excretion in the urine in the only two patients tested in this manner after the idea was conceived.

### Materials and methods

The red cell transketolase assay test described by Massod et al<sup>5</sup> was made available in 1972. From 1972 until February 1977 we performed 172 red cell transketolase assays in our laboratory. Blood samples were obtained from 73 apparently healthy subjects between the ages of 3 and 68 years. The range of TKA activity in these individuals was 44.5 to 87.6 mU/L/min, mean  $63.54 \pm 13.06$  (SD). The results were consistent with those reported by Massod et al. The range of TPPE was from 0% to 15.4%, mean  $4.42 \pm 4.47$  (SD). Massod et al reported considerable differences in the activity of the enzyme when a phosphate buffer was used and compared with glycylglycine. The values reported here from our laboratory were obtained by using glycylglycine in the assay system.

### Case reports

**Case 1.** A 3-year-old Caucasian boy with a history of episodes of heart palpitations and cyanosis was referred to the Cleveland Clinic. His mother had severe toxemia in pregnancy necessitating induction of labor. The patient had no suck reflex for 2 weeks after birth. At 5 months of age repeated vomiting was treated with changes in milk formula, and serous otitis media was treated with aeration tubes. Early development was normal. At 2½ years of age he experienced a 10-minute episode of palpitation. Thereafter, he had similar episodes monthly and then every other week. He was described as becoming pale, sweating, and weak; cardiac

impulse was visible, and he would become cyanotic. On at least one occasion he was admitted to a local hospital. His most recent attack had lasted several hours and oxygen therapy was required for 36 hours. System review revealed that he had large tonsils, slept 15 to 16 hours of every 24 hours, had nocturnal fever, snored, talked in his sleep, had abdominal pain frequently, and had edema around his eyes. His father was diabetic and the paternal grandmother had "swollen eyes since infancy." The mother had persistent leg edema and had experienced abdominal bloating. Apart from enlarged tonsils and a functional heart murmur, results of the examination were normal. Blood pressure was 98/0 mm Hg. Tonsillectomy was performed, and because of abnormal TPPE, a supplement of thiamine hydrochloride, 150 mg/day, was started. One month later he had no further autonomic dysfunction but still had recurrent abdominal pain. He slept well, did not snore, and his general activity was improved. Blood pressure was [74/40]30 with a distinct phase change at 40 mm Hg. Two months after surgery, thiamine was discontinued and the child rapidly became irritable, lethargic, and began to have a recurrence of sleep disturbance. Symptoms again disappeared after thiamine therapy was restored. The results of TKA and TPPE before and after therapy are listed in *Table 1*.

**Case 2.** A 22-month-old Caucasian female, the younger of two children, was examined because of sudden onset of seizures. Her sister had been under our care because of immunologic failure and organic brain

**Table 1.** TKA and TPPE values in four children before and after thiamine hydrochloride therapy

Case	Before treatment		After treatment		Time interval, mo
	TKA, mU/L/min	TPPE, %	TKA, mU/L/min	TPPE, %	
1	58.29	16.42	42.20	2.50	1
2	65.86	18.19	42.09	0	2
3	31.85	21.95	68.53	0	2
4	64.37	23.70	72.24	0.48	2

disease of unknown cause. The birth history and early development were normal. One week previously, she had a voluminous diarrheal stool followed by protracted vomiting which continued for 12 hours. She became apathetic and lethargic, and vomiting and diarrhea continued intermittently for 4 days, after which she became extremely fatigued and apathetic. She appeared to have an unsteady gait and held onto things as she walked. She then experienced a grand mal type of seizure, and became cyanotic and apneic. She was admitted to a hospital where a second seizure occurred and "sighing" respirations were observed. Abdominal distension and pains, anorexia, and emotional irritability persisted. Results of physical examination were normal. The electroencephalogram was normal. Because a paternal uncle of this child was known to have intermediate serum alpha-1-antitrypsin inhibitory capacity, the study was requested on the patient. Serum revealed an antiinhibitory capacity of 438  $\mu\text{g/ml}$ , in the heterozygous range of deficiency in our laboratory. Because of abnormal TKA and TPPE values, a supplement of thiamine hydrochloride, 150 mg/day, was prescribed. She was examined again 2 months later and was clinically well. Laboratory studies including urine for creatine, creatinine, and uric acid, and TKA and TPPE were repeated. Serum alpha-1-antitrypsin inhibitory capacity was 1555  $\mu\text{g/ml}$ , in the normal range (800 to 1300  $\mu\text{g/ml}$ ).

**Case 3.** A 3-week-old Caucasian female infant was referred to the Cleveland Clinic because of episodes of apnea. Birth history was normal. The first week after birth she slept almost constantly and had to be awakened, with difficulty, for feeding. On the sixth day of life, she suddenly became pale and apneic during a diaper change; she was "rag limp," and defecated and urinated. Her extremities and lips became cyanotic, and her mother administered mouth-to-mouth resuscitation. No abnormality was found on examination at a hospital emergency room. A similar episode occurred 2 days later, and she was admitted to the Cleveland Clinic and connected to a cardiorespiratory moni-

tor. Shallow, irregular respirations were observed during "sound sleep" and nasal congestion, rhinorrhea, and diarrhea developed. Stools were described as "green and seedy." Some respiratory wheezing was noted. On examination she was observed to be unusually quiet but arousable. Heart rate was 170 beats per minute, and the blood pressure 70 mm Hg by flush. The abnormal TPPE and TKA levels are shown in *Table 1*. A supplement of thiamine hydrochloride, 150 mg/day, was begun, and she was discharged from the hospital. Cardiorespiratory monitoring was maintained at home and, apart from one episode of apnea and some intermittent abdominal distension, and the unusual sleep pattern which persisted, she was normal. Poor neck tone was observed, but otherwise the results of the physical examination were normal. She was noted to be unusually sensitive to noise. At the age of 6 months she was free of apnea but continued to be soporific, and occasionally wheezing would be heard. Neck tone was normal. For more than 9 months the mother had been trying to obtain the services of a repairman to investigate a leak in the gas line of the hot water tank in the home. When the infant was 7 months of age the leak was found to be dangerously large, and after it had been corrected the mother's headaches disappeared and the infant's sleep pattern became normal, suggesting that chronic carbon monoxide poisoning was a factor.

**Case 4.** A 9-year-old Caucasian boy was examined because of "nervousness." On a visit to the dentist he complained of stomachache and became so fearful that the examination had to be curtailed. Two months previously he had experienced gastroenteritis which had been followed by a radical change in personality. He lacked his previous self-confidence, became hesitant, and cried easily. He had several episodes of periumbilical pain lasting a few minutes at a time, and his appetite diminished. Night terrors, night awakening, sleep restlessness, and "gaspings" had been observed during sleep and after exercise. He sweated profusely. The diet history disclosed that he had been drinking a great deal of sweet beverage

and eating a large amount of candy. On examination he was extremely nervous. There was marked cardiac sinus arrhythmia and dermatographia. Abnormal TKA levels and ketoaciduria were accompanied by complete absence of urinary alanine by amino acid paper chromatography. A supplement of thiamine hydrochloride, 150 mg/day, was begun. He quickly lost his craving for sweet things, participated better in class, and lost his sense of fear. After an initial, small weight loss, his body weight increased from 34.8 kg in September to 37.3 kg in November. He was then asymptomatic; he slept well and had normal appetite and activity. His school work was excellent.

**Results**

Of 173 tests performed in our laboratory, 91 were normal for both TKA and TPPE. Of 44 studies reported with elevated TPPE levels and therefore pathognomonic of cocarboxylase deficiency, 13 were patients on the psychiatry service. TKA values were above normal in two patients. *Table 1* lists TKA and TPPE results in the four cases before and after treatment; *Table 2* lists concentrations of creatine, creatinine, and uric acid before and after thiamine therapy in two of the four patients.

**Discussion**

The four cases, though widely different in clinical expression, may have had chronic hypoxia of brain stem in common. The first case illustrates a relatively newly recognized entity, the sleep apnea syndrome. Enlarged tonsils and adenoids in children have long been associated with snoring, sleep disturbances, and nonspecific health changes such as failure to gain weight or poor appetite. A long-term complication of hypoxia can be cor pulmonale; sleep hypoxia is also considered to be an important factor in sudden infant death syndrome (SIDS).<sup>6</sup> Symptoms in one

**Table 2.** Urinary 12-hour day and 12-hour night excretion of creatine, creatinine and uric acid in two pediatric patients before and after treatment with thiamine hydrochloride

Case	Values before thiamine HCl										Values after thiamine HCl					
	mg/12 hr			mg/kg/24 hr			mg/12 hr			mg/kg/24 hr			mg/kg/24 hr			
	C	CR	R	UA	C	CR	UA	C	CR	R	UA	C	CR	UA		
1	Day, 12 hr	63	58	1.09	43	...	...	...	371	159	2.30	214	...	...		
	Night, 12 hr	50	95	0.53	92	...	...	46	194	0.24	86	...	...	...		
	Total, 24 hr	113	153	0.73	135	7.9	10.8	9.5	417	353	1.18	300	28.6	24.2		
2	Day, 12 hr	6	69	0.08	145	...	...	...	55	89	0.60	146	...	...		
	Night, 12 hr	13	47	0.30	79	...	...	...	33	95	0.35	68	...	...		
	Total, 24 hr	19	116	0.16	224	1.7	10.2	19.6	88	184	0.48	214	7.5	15.6		

C = creatine; CR = creatinine; R = ratio of creatine to creatinine; UA = uric acid.

patient (case 1) were dysautonomic, a phenomenon now known to be relevant in recognition of an infant at risk for SIDS.<sup>7</sup> Although tonsillectomy was helpful, presumably because it relieved the airway obstruction, as does a nasopharyngeal tube in the sleep apnea syndrome,<sup>6</sup> improvement in activity and undue fatigue were not observed until the vitamin supplement was offered. Restlessness when asleep and fatigue rapidly returned when thiamine therapy was discontinued some months after surgery and just as rapidly disappeared when the supplement was restored.

The second case strongly suggested that genetic factors were involved. The older sister, who had been under our care earlier, had a baffling array of clinical and laboratory abnormalities, which indicated that the severe delay in development was associated with partial immunologic paralysis. Ketoaciduria was suggestive of a possible thiamine-responsive encephalopathy,<sup>8</sup> but empirical trial produced no evidence of improvement, possibly because organic change was too advanced. The transketolase assay was not available at that time. A high ratio of creatine in urine was an interesting later observation and gave rise to a subsequent similar study in the younger sister (case 2). Several features in this case may be important. The paternal uncle was under the care of another physician at the Cleveland Clinic. He was being treated for Wilson's disease but ceruloplasmin assays were not consistently low and serum alpha-1-antitrypsin inhibitory capacity was in the heterozygous range of deficiency. The interest in our case was that her serum alpha-1-antitrypsin inhibitory capacity was in a similar range, but increased into the normal range as the TPPE decreased to zero. This was matched by increased urinary creatine

and creatinine levels as well as clinical improvement in appetite, overall activity, and disappearance of abnormal fatigue. Perhaps the genetic link in this family was an unusual need for thiamine related to chronic marginally defective energy metabolism that could be put into crisis during increased environmental stress such as infection.

The infant (case 3) behaved like an infant at risk for SIDS. The early presenting symptoms and the sex, although not major factors in themselves, were unusual for threatened SIDS,<sup>9</sup> which tends to affect males more than females between 1 and 5 months. The unusual sleep pattern and the mother's headaches may have been related to chronic carbon monoxide poisoning, and the changes in thiamine-dependent transketolase partially arising from hypoxic stress. The fourth case may be important nutritionally since this 9-year-old boy was consuming a large amount of carbohydrate, sometimes known as "junk food." It has long been known that caloric uptake, particularly carbohydrate, is closely tied to thiamine metabolism. It is possible that the exceedingly high intake of "naked calories" consumed by many children is insufficiently supported by the biochemical principle of oxidative capacity, perhaps analogous to a choked internal combustion engine. The well-known ketoaciduria which develops in thiamine deficiency might then be a reflection of calories ingested in proportion to the cellular ability to oxidize them completely. In other words, normal ingestion of thiamine would be inadequate if the caloric load is excessive.

Only two of these patients were evaluated for urinary creatine, creatinine, and uric acid, because the other two were evaluated before this study was conceived. In one patient (case 1) there

was a fourfold increase in 24-hour creatinine and a twofold increase in creatinine, reflecting a sharp rise in the ratio. There was also a doubling of uric acid concentration. In another patient (case 2) much the same thing was observed in creatine and creatinine, but there was no change in uric acid. The changes by day and night were different and may reflect metabolic differences in the waking and sleeping states. Little attempt has been made to use the relation of creatine to creatinine in assessing the complicated mechanisms of energy balance. Creatine is synthesized in kidney and liver and is a direct result of oxidative metabolism. It is a molecule that carries a nonlabile methyl group, a most important factor since it does not take part in transmethylation. It is carried in blood and passes through the cell membrane of muscle where there appears to be an active transport system.<sup>10</sup> It then uses adenosine triphosphate to form creatine phosphate. Although creatine phosphate is used for synthesis of adenosine triphosphate, the source of power at the contractile site, it is not itself a direct participant in the endergonic reaction, although its presence appears to be a vital link for reasons that are presently unknown.<sup>11</sup> Creatinine is formed nonenzymatically mainly from creatine phosphate.<sup>12</sup> By measuring these two nitrogenous compounds in urine, there are several possible interpretations which can be applied. (1) It may reflect an increased synthesis of creatine, although so far none has succeeded in demonstrating this as a mechanism.<sup>10</sup> (2) It might reflect defective uptake by muscle, possibly in cases where the transport mechanism is damaged, or the "trapping" mechanism for the formation of creatine phosphate has failed.<sup>10</sup> These two mechanisms have been extensively studied and so far have been the

only ones thought to occur. (3) It might reveal malfunction in the renal tubular resorption mechanism.<sup>10</sup>

Creatinuria occurs in hyperthyroidism induced in rats by injection of T-3.<sup>13</sup> Oxygen consumption increased in these animals to a peak 48 hours after injection, diminishing to preinjection levels at 96 hours. Urinary creatine increased to a maximum 34 to 48 hours after injection and decreased to preinjection levels at 72 to 82 hours after T-3 was given. Urinary creatinine decreased with time after the injection. Kurahashi and Kuroshima<sup>13</sup> deduced that the mechanism was related to increased creatine loss from muscle and decreased creatine uptake rather than increased synthesis. Creatinuria appeared to be directly proportional to oxygen consumption and presumably, therefore, uncoupling of oxidative phosphorylation.<sup>14</sup> Clark and associates<sup>15</sup> reported studies of urinary excretion of creatine and creatinine in children. They pointed out that urinary excretion of creatine is characteristic of childhood. It decreases with age as excretion of creatinine increases, suggesting slowly changing metabolism of the body as might be associated with growth. Urinary creatine excretion is extremely variable and the ratio of creatine to creatinine can exceed unity in the first 2 years. Perhaps the only way to evaluate it in a given patient is on a dynamic basis, attempting to correlate it with clinical symptoms and signs and rate of growth. The question of thiamine deficiency as an important etiologic factor in our four cases must be viewed strictly from a biochemical interpretation. We have suggested that hypoxic stress from carbon monoxide poisoning in one patient (case 3) was the primary factor. Although hypoxia has been reported as a factor in SIDS,<sup>16</sup> the cause is usually

obscure. Beriberi victims were known to have low arterial and high venous oxygen saturation,<sup>17</sup> and sometimes sudden death was suspected of being caused by central failure of cardiorespiratory control.<sup>18</sup> Fehily<sup>19</sup> reported sudden infant death in Hong Kong due to B<sub>1</sub> avitaminotic breast milk. These deaths ceased when the rice ration to nursing mothers was curtailed and reappeared when their ration was increased, suggesting that there was an important association with "naked calories." Lonsdale<sup>20</sup> compared the epidemiology of this syndrome with that of modern SIDS. It was shown that hemorrhagic shock, produced experimentally in dogs, lowered cocarboxylase activity and could be partially corrected by giving large doses of thiamine.<sup>21</sup> Skelton<sup>22</sup> produced Selye's general adaptation syndrome in rats by making them thiamine deficient, and Naeye<sup>23</sup> reported cor pulmonale and hypoventilation syndrome in a man who had early Wernicke encephalopathy at autopsy. It is suggested that it is the chemical factor of the redox principle which is compromised, whether it be suffocation, rarefied ambient oxygen concentration, deficiency of intracellular glucose, or lack of catalyst.

In these four cases, no therapy other than the thiamine supplement was used. It is not possible to say whether an alternative method would have been more or less beneficial. The TPP effect is highly specific in that transketolase activity is either influenced or not influenced by the addition of its cofactor. Results of animal studies have shown that this effect is the most precise method of detecting thiamine deficiency in the cells used for the assay,<sup>24</sup> and when the laboratory correction coincides with the patient's clinical improvement, it is not unreasonable to assume

cause and effect. Far from assuming that the etiology is dietetic in origin, consideration must be given to many, possibly quite nonspecific factors including unusual dietetic need, malabsorption, abnormal biochemical activation, or unusual utilization because of an accelerated metabolic response to stress.<sup>25</sup>

A close relation between transketolase and the "stress" of pregnancy has been reported.<sup>26</sup> That diet is accepted as adequate can be misleading. This was the case in the infant in whom Wernicke encephalopathy developed while receiving a soya bean formula.<sup>27</sup> We have not been able to find any publications on abnormal TKA in American children, since thiamine deficiency is hardly ever considered in differential diagnosis. In normal Thai infants and children, TKA was reported as  $75.6 \pm 20.5$  IU and TPP effect  $6.6 \pm 5.1\%$ .<sup>28</sup> Transketolase activity has been investigated in various clinical conditions and the results showed that adult control values did not differ from those in patients with collagen disease, diabetes, and Addisonian anemia. Partially gastrectomized patients had TKA values lower than controls.<sup>29</sup>

### Summary

Four children are described with various symptoms which may have arisen on the basis of a common biochemical theme. Abnormal TKA or TPP effect or both were corrected by the administration of a thiamine supplement. This biochemical correction corresponded with clinical improvement, and in two of the children changes in creatine and creatinine values suggested an improvement in oxygen utilization. Nutritional deficiencies not presently recognized may well be responsible for a considerable amount of ill health.

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