Clinical Trials with Thiamine Tetrahydrofurfuryl Disulfide (TTFD) in Down's Syndrome

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A clinical trial with megadose vitamin supplements reported benefit in some children with Down's syndrome.[1] Since that time at least one study[2] of a similar nature was reported to show no effect. However, this study did not follow the same protocol as Harrell and Associates, since no thyroid was administered. Thiamine tetrahydrofurfuryl disulfide (TTFD), a synthetic allithiamine, has been shown to have some therapeutic effects which strongly suggest that it enhances the physiologic actions of acetyl choline,[3] * is partially protective against cyanide poisoning in mice,[4] and has marked physiologic effects upon isolated animal heart.[5] Thiamine propyl disulfide, another synthetic allithiamine, is more effective than thiamine hydrochloride in the treatment of alcoholics.[6] Absorption of TTFD and thiamine propyl disulfide into tissues, including brain is better than that of the water soluble vitamin.[7]

Recent work[8] has reported cholinergic deterioration in Alzheimer's disease. Brains of middle aged Down's syndrome subjects reveal pathology similar to that seen in this disease.[9] It has been pointed out that children with Down's syndrome are dysautonomic, and that pupillary reflexes suggest loss of cholinergic neurotransmission.[10]

These facts suggested that a fundamental defect in Down's syndrome might be loss of efficiency in redox and that oxidative metabolism is the real key to understanding the multitude of mental and physical problems that affect these individuals. Since beriberi represents the prototype model for acquired dysautonomia,[11] and abnormal transketolase activity has been reported in Down's syndrome,[12] it seemed logical to attempt a clinical trial using this very active derivative of the thiamine molecule.

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Patients and Methods

Twenty-two children with Down's syndrome completed the study. There were 8 males and 14 females. The subjects were all between the ages of 8 and 16 years, since it was decided that the age group might be relatively more cooperative and represent a more uniform problem in IQ testing. Otherwise they were recruited at random by contacting local agencies. Each subject was age and sex matched into two groups. Group 1 received authentic TTFD for a full year. It was decided that the placebo group, group 2, should be exposed to authentic TTFD for at least part of the experiment, since it is completely nontoxic in our own experience and that of others.[6 7]

Assignment to groups was made at random by a study coordinator, and the parents and clinical investigators were blind to the assignment. In seeking informed consent, the parents were told that their children might be in one or other of the two groups, but if assigned to the placebo group there would be a switch to authentic TTFD at 3, 6, or 9 months into the clinical trial. In practice, all the children in group 2 had 6 months placebo and 6 months TTFD in order to obtain a degree of uniformity. Packages of tablets were prepared by Tak-eda Chemical Industries and both authentic TTFD and placebo were identical in appearance, made up as bright yellow enteric coated pills. Parents were given sufficient material to last exactly 3 months so they were unaware of the fact that the switch was made at 6 months. To avoid the potential problem of single nutrient administration each subject in both groups received a single tablet of a multivitamin, multimineral preparation throughout the

year. It was considered unlikely that this would have any therapeutic effect by itself, particularly as other investigators had reported a negative response to megavitamin dosage.[2] On the other hand, we have experienced some disadvantage in the clinical response of some patients if TTFD is given as a single nutrient (Lonsdale, D.: unpublished observations).

Each subject received an initial IQ test, and a hair analysis. A clinical photograph was made of the face in order to document any clearcut visible change that might occur. The IQ test was repeated after 6 months and again after a second 6 months. Hair analysis was repeated at one year, but not at six months.

The dose of TTFD used was 50 mg in divided doses, given three times a day. Parents were provided with a "symptom inventory" form which enabled them to record the appearance or disappearance of any one of a specified list of symptoms, with room to record any symptoms that did not appear in the list. The listed symptoms were chosen because they are those expected in dysautonomic function and may not have been noted by the parents unless specifically requested.

The senior clinical investigator had no contact with the subjects at all throughout the study, the assessment being made entirely from the symptom inventory, the IQ ratings, and telephone contact with parents to discuss their report in the symptom inventory. In one or two cases a teacher report was received at the request of the parent. Compliance was difficult to control and every effort was made by the study coordinator to encourage parents to follow the simple instructions. In spite of this there was evidence of clandestine noncompliance in some cases which may or may not have been significant. In such cases of delinquency it amounted to irregular administrations of tablets, and failure to record facts in the symptom inventory.

IQ Testing

The Wechsler Intelligence Scale for Children — Revised (WISC-R) was used for those subjects below the age of 16 years throughout the study. The Wechsler Adult Intelligence Scale — Revised (WAIS-R) was used for those subjects who would be over 16 years at the end of the study. These two scales are comparable and are currently the best in assessing a variety of modes of intellectual function. They incorporate Verbal (VIQ), Performance (PIQ), and Full Scale Intelligence (FSIQ), which gives some insight into both verbal reasoning and perceptual awareness.

Within the Verbal Scale there are 6 subtests, Information (I) Similarities (S), Arithmetic (A), Vocabulary (V), Comprehension (C), and Digit Span (DS). The performance Scale is assessed by Picture Completion (PC), Picture Arrangement (PA), Block Design (BD), Object Assembly (OA) and Coding (Cod). Each subtest includes a time limit.

Kaufman[13] described 3 subtest clusters within the WISC known as Verbal Comprehension (V-C), Perceptual-Analytical (P-A), and Attention Concentration (A-C). Computation of the Kaufman clusters is obtained from conversion scores developed by Sobotka and Black.[14] Significance of WISC-R is determined from a mean of 100 and SD of 15, for VIQ, PIQ, and FSIQ. For each subtest the mean score is 10 with SD of 3. In clinical use a change of 10 points in any of the IQ scores, or a change of 3 in any subtest, is considered to be significant.

Results

Group 1 consisted of 11 subjects, 4 males and 7 females. Group 2 was similar, 4 males and 7 females. It was clear that no dramatic responses were observed in any of the 22 subjects. However, there was no question that some did show evidence of modest clinical improvement, either in general behavior or in terms of physical health.

The changes in psychosomatic features, when observed, were considered to be useful since they were not expected by parents (Table 1). In 4 group 1, and in 4 group 2 subjects there was clearly no response at all and they were easily classified as non-responders. Some kind of improvement was observed in 14, although IQ changes were seen in only 5. In group 1 there were 3 subjects whose IQ testing improved and 2 in group 2. These cases are considered

separately. The IQ scores are presented in Table 2. The changes in verbal, nonverbal, or full scale IQ changes for the 2 groups as a whole were not significant.

GROUP 1

There were definite improvements in 3 subjects. In case 2, an eleven year old boy, there was an increase of more than 12 score points in the PIQ and 11 points in the FSIQ, both significant. Although there was no increase in the VIQ, there was an increase of 4 points in both PC and BD which reflected improvement in visual discrimination and analysis, and synthesis of visual patterns in constructing block designs.

Case 6 was a sixteen year old girl at the beginning of the study. Subtest PC and OA scores increased by 3 points each, demonstrating improvement in visual discrimination, and visual memory. This reflected an increase of 11 points in PIQ which is significant.

Case 22, an eight year old girl, had increases in BD and OA subtests which reflected in an 18 point increase in PIQ from 46 to 64. As a result, the FSIQ increased 11 points. There was also an improvement in the S subtest which increased the VIQ, though this was not significant.

GROUP 2

There were 2 patients in this group that showed some improvements by the end of the year, though not significant. In case 9, a fourteen year old girl, the PA score increased by 4 points, indicating improved visual sequencing and social perception. The FSIQ increased 7 points over the year. In case 13, an eleven year old girl, there was a 5 point increase in FSIQ.

In 4 subjects out of group 1 there were some clinical improvements reported but with no discernible changes in IQ tests.

CASE 3: (F) The teacher reported improved attention span and reading capability.

CASE 17: (F) The entire family reported increased social awareness and comprehension. The clinical photograph, assessed by several independent observers, supported this since the correct photograph was chosen in representing appearance before and after the study.

CASE 18: (M) parents reported improved comprehension and communication.

CASE 19: (F) A school psychologist reported an increase from 20 to 26 months on the Development Index on the Bayley scales of index development. She was un-testable for IQ assessment.

In group 2 there were 5 subjects who demonstrated some observed improvements, but without any change in IQ. From the symptom inventory these improvements correlated with the second half of the year.

CASE 5: (F) Sleep restlessness, insomnia, frequent awakening and irregular sleep breathing improved.

CASE 8: (M) Parents knew from his behavior when he was switched from placebo to authentic TTFD. Hyperactivity, temper tantrums, sleep restlessness, insomnia, frequent awakening, constipation and urinary frequency all became more marked after beginning TTFD and then improved. The clinical photograph suggested improved alertness.

CASE 12: (M) Parents observed improved response to instruction. The teacher commented on improved school performance.

CASE 14: (M) Parents reported increased comprehension and independence. Sleep sweating, insomnia and night terrors increased temporarily. There was a marked increase in appetite. A general improvement was observed 3 months after beginning TTFD.

CASE 20: (F) A personality improvement was reported 2 months after beginning TTFD.

Hair Analysis

Results from hair analysis were extremely variable. The most striking feature was the degree of change observed. This, in our experience, is not usually observed in every day clinical practice. Table 3 presents a summary of variable changes observed in the concentration of heavy metals. The exception to this was the hair mercury concentration which decreased significantly in 17 out of the 22 subjects. It remained the same in 3, but the initial

analysis was not elevated. In two subjects there was a slight rise in mercury, from 43 to 53/ug/100 g hair in one and from 64 to 80/ug in the other. Table 4 shows the mean concentration of mercury in the initial and final analysis and the difference between the two. Values are shown for the total number of subjects in each group and the "responders" are compared with the "non-responders."

Discussion

There were 7 subjects in each group who were of potential interest, though it was quite clear that no major improvements were observed. In 8 there was no response at all. In 3 group 1 and 2 group 2 subjects, there was demonstratable improvement in IQ rating, but parents indicated that they saw no behavioral change to support this.

There are several comments required. Down's syndrome victims are each unique individuals metabolically and cannot be put together in a group as is conventional in many studies. It is likely that the different nutrients are more likely to be beneficial to different subjects, just as in normal people. So the investigators in this study did not expect a uniform response. As in every experiment performed on retarded subjects there is considerable difficulty in proving or disproving efficaciousness of a nutrient such as TTFD. Like all agents of this type, the dose for the individual is not known, and the time factor is probably extremely variable. Add to this, the problem of "paradoxical" temporary response where the subject exhibits worsening of the symptoms, a phenomenon regularly observed by us in beginning any form of nutritional therapy. Experiments with treatment of hypertension in SHR rats using TTFD showed lack of uniform response in the group since some animals were responders and others were not.[15]

Down's syndrome subjects are severely affected by a distortion of their genetic balance, and a nutritional approach can only provide compensatory improvement in redox at the best. These subjects were recruited at random, using only the simple fact that they were all affected with Down's syndrome and without differentiating them by age or by IQ rating. All of them were severely retarded. In spite of this it seemed that there was definite if modest improvement observed in a surprising number of these individuals.

There is evidence that dysautonomic function is a regular feature observed in this syndrome. Lejeune[10] has pointed out that their pupillary responses show cholinergic denervation, and it is therefore not surprising that Alzheimer's disease is relatively common in these people, since the evidence is accumulating that Alzheimer brains are cholinergically deficient. The best clinical model for dysautonomic function is familial dysautonomia[16] and we used this model to enumerate the symptoms that could be classified as dysautonomic in our test subjects. Riley et al.[17] reported patients with incomplete forms of dysautonomia and autonomic failure of varying degree is surprisingly common in many different conditions.[18] We believe that such symptoms that were observed in this study were centrally mediated and could be used to gauge a positive response to the agent used, in this case, TTFD. Thus the appearance, and subsequent disappearance, of such symptoms in some of our study subjects was important, particularly as the parents who recorded them were quite unaware of their potential significance.

A surprising and frustrating feature in this study was the relative lack of interest exhibited by the parents. Symptom inventories were poorly filled in and some of the subjects received irregular administration of tablets. It may be that overwhelming pessimism played a part, since our approach may have seemed too simple and inexpensive. In retrospect, it would have been better to deny the group 2 subjects any TTFD for the full year, for this would have produced two pure populations to compare. The modest improvements seen in this group did correlate with the second half of the one year study, but the ability to test definitively was not accurate enough. Nevertheless, we believe that there was enough observed response to make this agent of interest in repeating a similar study, perhaps in much younger patients where the success might be greater.

Hair analyses were chiefly remarkable for the extreme changes observed, even though they did not follow a repetitive pattern. There does, however, appear to be a trend in hair mercury in those subjects in whom this metal was found to be relatively elevated. It is also interesting that the decrease in this heavy metal was greater in group 1 patients compared with group 2, although there was inconsistency in comparing "responders" with "non-re-sponders."

Table 1

	Group I				Group II			
Symptom	**Number of Cases**	**IMP**	**Worse**	**Same**	**Number of Cases**	**IMP**	**Worse**	**Sar**
Hyperactivity					1	1		
Hypoactivity	1			1	4	2	1	1
Tantrums	1		1		3	1	2	
Restless Sleep					5	2	1	1
Sleep Sweating					2	1	1	
Insomnia					3	1	2	
Frequent Awakening					3	1	2	
Night Terrors					1		1	
Sleep Talking	2		1	1	2	1	1	
Bruxism	1	1			1			1
Sleep Breathing Irregular					3	1		2
Rapid	1			1				
Slow	1			1	2			2
Comprehension	11	6		5	11	4	2	5
Compliance	2	1	1		7	2	3	2
Negativism	2	1	1		4	2	2	
Mood Swings					3	1	1	1
Noise Sensitive	1			1	3	1		2
Nasal Congestion	2	1	1		8	4	2	2
Nervous Cough					2		1	1
Frequency of Urination					1	1		
Tachycardia	1			1	2	1		1
Appetite	3	3			6	3	1	2
Recurrent Vomiting	1							
Diarrhea	1							
Constipation	1			1	4	1	1	2
Recurrent Colds	1				6	3	1	2
Ear Infection	1				2	2		
Throat Infections	1				2	1		1
Poor Cold Tolerance	1				2			2
Poor Heat Tolerance	1			1	2		2	

Symptom inventory summary from both groups of subjects.
Many of the somatic symptoms were recorded in the same individuals.

Table 2

Group	Case	1st VIQ	1st PIQ	1st FSIQ	2nd VIQ	2nd PIQ	2nd FSIQ	% INC	3rc 1 VIQ	3rc 1 PIQ	3rc 1 FSIQ	%INC (FSIQ)
I	2	50	45		41	50	49	45 + 9.7	55	57	57	+26.8
	6	59	53		54	57	58	55 + 1.8	58	64	60	+11.1
	22	45	46		40	45	40	40 0	47	64	51	+27.5
II	9	49	45		40	58	45	44 + 10	55	46	47	+17.5
	13	47	49		44	46	55	46 + 4.5	50	57	49	+11.4

Results of IQ testing in 5 patients. Percentage increase is based upon the prestudy testing. Tests were repeated at 6 months and a year.

TABLE 3

	Group I Increase	Group I Decrease	Group I Same	Group II Increase	Group II Decrease	Group II Same
Lead	6	5	0	3	6	2
Mercury	1	10	0	1	7	3
Cadmium	2	5	4	1	3	7
Arsenic	3	7	1	2	7	2
Aluminum	5	5	1	2	8	1

Results of heavy metal changes in concentrations seen in hair of 22 subjects. Samples were taken before study beg an and after 1 year. **Table 4**

	Initial Analysis ug/100 G hair	Final Analysis ug/100 G hair	Mean Difference
Total Group	85.2	35.4	49.8
Responders n = 14	88.6	38.9	49.7
Non Responders n = 8	79.4	29.1	50.3
Group I n = 11	111.6	42.9	68.7
Group II n = 11	58.8	27.8	31.0
Group I "Responders" n = 7	111.6	47.4	64.2
Group I "Non Responders" n = 4	111.7	35.0	76.7
Group II "Responders" n = 7	65.6	30.4	35.2
Group II "Non Responders" n = 4	47	23.2	23.8

Analysis of mercury content of hair in all 22 subjects. Figures show initial, final and difference in concentration.

Conclusion

This study did not reveal any dramatic response in any of our 22 subjects. Although 5 of them did demonstrate some increase in IQ ratings, there was little change in the behavior to encourage the parents in most cases, though there were some observations which were somewhat open to objective bias. There were some factors that may have made a difference, namely the length of time of administration and the dose. In a group of severely handicapped patients, any improvement is helpful and there was enough evidence of this in some of these subjects to make it worthwhile to pursue the nutrient approach further.

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