A Case of a Rare Genetic Disorder and its Clinical Responsiveness to Naturopathic Treatment

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Abstract

Genetic disorders, or syndromes, in this case an autosomal deletion, are often manifested by peculiar phenotypic expressions or characteristics. In this paper, a review of a case in which specific nutritional intervention has produced promising early results raises the possibility that detailed analysis of metabolic functioning may provide an avenue to possibly circumventing, or at least minimizing, some of the manifestations expressed in genetic disorders.

CASE STUDY

J.V. is a Caucasian male child, born on March 26, 1995. He was first presented at my office in early August of the same year. He appeared to be like a newborn. At just 10 lbs, 8 oz, he had gained only 2.5 pounds in the five months of life prior to his first visit. Due to his young age and because both parents were patients of mine, my unofficial opinion was requested. Detailed initial history and examination were not performed, but results of prior medical evaluation were reviewed and an informal discussion of the pertinent points of the case occurred. He had been under medical care and supervision since birth and the doctors had failed to find any significant pathological abnormality. Being born eighth of eight children to a 46 year old mother, specific concerns needed to be addressed and were. Failure to thrive was ruled out. Neglect had been investigated but proved unwarranted. The parents were very loving and caring individuals and did what they could for the child. Concerns of malnutrition or of inadequate mother's milk seemed the most plausible explanation to his physicians and suggestions of supplementing his diet with formula had been made.

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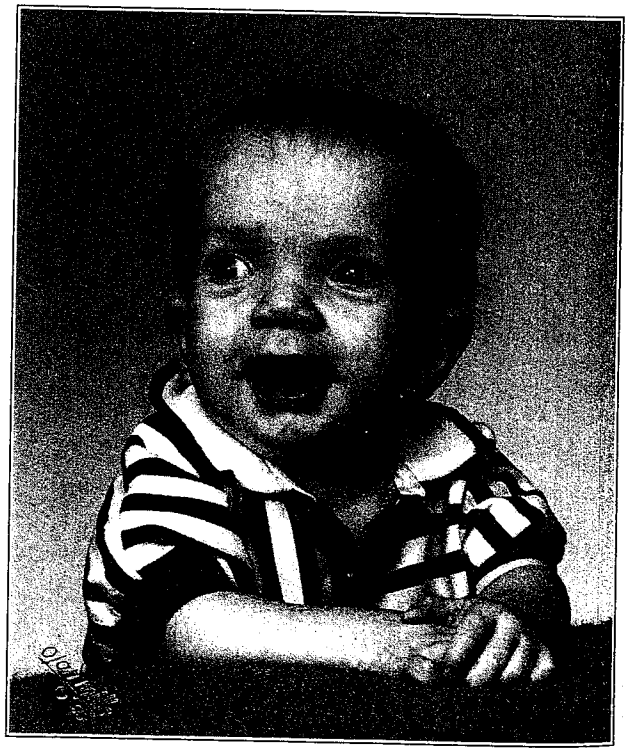
Medical records indicate J.V. was born at 8 lbs 2 oz and had a length of 21 inches, both within normal limits. His Apgar scores

Before Supplements



were 9 and 10 respectively. The pregnancy was complicated only by a severe viral illness which his mother suffered approximately one month before term and by there being a calcified placenta of no apparent clinical significance at birth. His newborn health screening at five weeks of age was considered normal. From this point on, J.V. progressively fell behind the normal growth curve according to the National Center for Health Statistics (NCHS) Physical Growth Percentiles. Medically classified as having a mild developmental delay, J.V.'s appearance raised some questions as to whether an underlying pathology existed. Medical examination revealed dysmorphic features, or facial asymmetry, with a wandering or lazy eye. His interpupilary distance was large at 5.5 cm. He had slightly asymmetric ears, round facies and a short stature. His nose was considered wide and had prominent alae nasae. Obvious hypotonia was marked. Muscular dystrophy was an early consideration, as was Down's syndrome, but without immediate family history or diagnostic confirmations, these diagnoses were later discarded. A myopathic disorder was finally given as a generic diagnosis since his muscular development was obviously arrested.

At the time of his first visit to my office, J.V. had not developed any locomotion skills of his own nor did he possess the strength to hold himself erect or upright. Previous and subsequent medical history included: regular pediatric development evaluation, including height, weight and head circumference measurements; regular physical examinations and review of organ systems; a cranial CT scan. Lactate and plasma organic acid analyses were also performed to rule out any metabolic disorder and found to be unremarkable. Ophthalmological examination revealed bilaterally small optic nerves, but no tests or examinations revealed any pattern of diagnostic significance. He was referred to the division of medical genetics at the University of Iowa Hospitals and Clinics. No specific syndrome was initially recognized; however, a diagnosis was made after chromosomal analysis of a peripheral blood sample. J.V. was suffering from a relatively rare genetic syndrome called 18p deletion (18p-) syndrome.

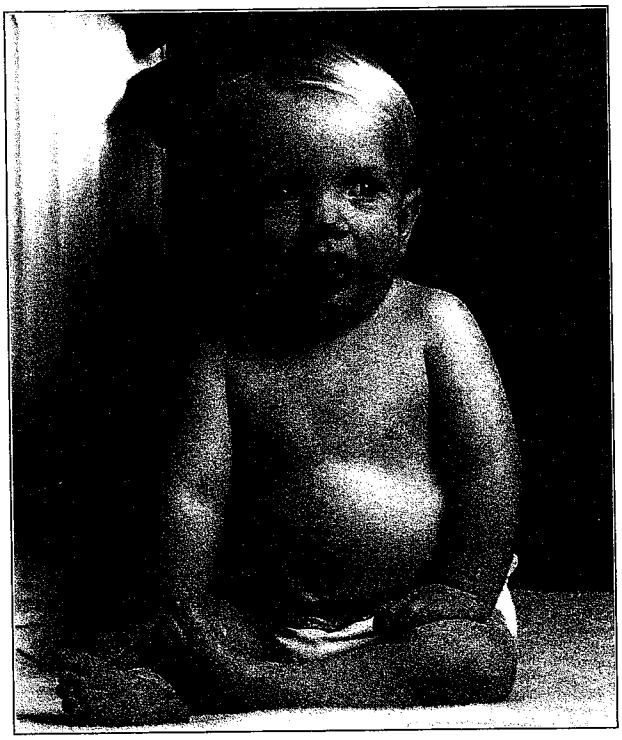
Diagnosis was made following stimulation of J.V.'s blood lymphocytes with phytohemagglutinin which were then synchronized to obtain elongated chromosomes after first being cultured for 72-96 hours. Arresting further cell division by the use of colcemid, the chromosomes were then stained utilizing the G-Banding method. Microscopic analysis and karyotyping were then performed. A deletion in the short arm of chromosome 18 was observed.

Deletion of the short arm of chromosome 18, or 18p- syndrome, was first observed by de Grouchy, et al, in 1963 (1). According to The Chromosome 18 Registry & Research Society in San Antonio Texas, 102 families have reported cases to date (2). Abnormalities of chromosome 18 include a wide range of disorders. 18q- (deletion of the long arm of chromosome 18), 18p- (deletion of the short arm) and ring 18 syndromes (part of the chromosome has formed a ring) have a combined frequency of approximately 1 in every 46,000 births making them some of the more common autosomal deletion disorders (3). Most of the deletions occur during spermatogenesis/oogenesis, or possibly during early embryonic development. Parents are often requested to be studied to determine if either is a balanced translocation carrier; however, both refused evaluation in this case. There has been a greater than 60% female predominance observed in 18p-, with mean parental ages of 31.3 years for the mother and 35.7 years for the father (4). Broad variability in the phenotype has been observed.

The most common, or consistent, feature abnormalities include: a mild to moderate growth deficiency or developmental delay (approximately 80% of cases); hypotonia (approximately 23% of cases); some abnormality in size, shape or location of the ear occurs in about 70% of cases (3). Holoprosencephaly, a developmental abnormality of the brain, has been observed in 67% of cases and mental deficiency or retardation has been recorded in approximately 98% of cases (3). IQs are said to range between 25 and 75 (4) with the average being 59 (3). Approximately 50% of cases have an IgA deficiency (often asymptomatic) and many are seen with small jaws and experience a high frequency of dental caries (3). Additional common phenotype characteristics seen include microcephaly, a short neck, a web neck, digit abnormalities, strabismus and ptosis (3,4). Eight percent develop hypothyroidism and rheumatoid arthritis (RA), or RA-like symptoms (3). Language ability is often delayed with many afflicted individuals not speaking simple sentences before the age of seven or eight (4). Behavioral problems are common, often manifested by a difficulty in or lack of concentration, a fear of strangers, restlessness and/or emotional volatility (4). An inability to form relationships has also been reported (3).

In September of 1995, after my initial consult with J.V.'s parents and prior to his final diagnosis, I felt adequate medical diagnostic procedures had been performed to date. No obvious condition had yet been found to explain J.V.'s poor linear

AFTER SUPPLEMENTS



growth and developmental delay. Metabolic function testing was discussed. I believed J.V. must have been suffering from some metabolic dysfunction which had severely limited his ability to grow both physically and neurologically. I suspected either a form of malabsorption or toxic exposure as the most immediately plausible causes. Due to the location of his home, the possibility existed for J.V. to have received xenobiotic exposure (the family operates a business where diesel fuel is constantly present). I believed challenge testing to be inappropriate, due to his small body weight, so our laboratory options were limited to a simple venipuncture, stool or urine collection. Several years earlier, I had heard mention of a study in which short stature for age children were found to have elevated serum lipid peroxidation (unfortunately, an intensive search for this publication was unsuccessful). I opted for an amino acid analysis and oxidative stress panel.

AMINO ACID ANALYSIS—INITIAL

ESSENTIAL AMINO ACIDS			
Arginine	42 nmol/l	L	60-160
Histidine	44	L	60-140
Isoleucine	41	L	50-160
Leucine	78	L	95-230
Lysine	81	L	130-340
Methionine	14	L	20-50
Phenylalanine	37	L	55-140
Threonine	41	L	100-250
Tryptophan	8	L	20-60
Valine	117	L	150-420
ESSENTIAL AMINO ACID DERIVATIVES			
Gamma-aminobutyric Acid	1		< 5
Glycine	92	L	180-450
Serine	86	L	100-210
Taurine	52		50-250
Tyrosine	37	L	50-120
AMMONIA/ENERGY METABOLISM			
a-Aminoadipic Acid	4	H	< or = 1
Asparagine	25	L	50-130
Aspartic Acid	4	L	5-30
Citruline	16		10-40
Glutamic Acid	24	L	30-150
Glutamine	530		450-1050
Ornithine	59		50-120
Sulfur metabolism			
Cystine	17		15-90
Cystathione	4		< or = 5
Homocystine	<1		< or = 1
ADDITIONAL METABOLITES			
a-Amino-N-Butyric Acid	4	L	30-70
Alanine	162	L	290-550
Anserine	< 1		< or = 1
B-Alanine	19	H	< or = 1
B-Aminoisobutyric Acid	< 1		< or = 1
Carnosine	< 1		< or = 1
Ethanolamine	4		< or = 10
Hydroxylysine	< 1		< or = 10
Hydroxyproline	13		< or = 75
1-Methylhistidine	< 1		< or = 20
3-Methylhistidine	4		< or = 5
Phosphoethanolamine	36		< or = 75
Phosphoserine	13	H	< or = 12
Proline	106	L	130-400
Sarcosine	< 1		< or = 1

TABLE 1

Initial results revealed lipid peroxides at 6.3 nmol/ml (ref. range: 0 - 3.4) and marked deficiencies in all of the essential amino acids (see Table 1). Low levels of essential amino acids in blood plasma can reflect poor digestion and assimilation of proteins when diet is adequate (5). Specific deficiencies, such as phenylalanine, tryptophan and tyrosine, can also reflect inadequate stomach HCL, or pepsin proteolysis (5). Low lysine levels can inhibit transamination as it functions as the P5P (pyridoxal-5-phosphate) attachment site in transaminase enzymes (5). Lysine is needed in the formation of collagen, as well as in the synthesis of muscle protein and L-carnitine. Calcium utilization is greatly reduced when L-lysine is deficient (6). Lysine and arginine are potent promoters of mineral absorption and have been shown to enhance the incorporation of calcium into bone matrix by nearly twofold, while lysine supplementation has been found to markedly reduce the incidence of dental caries in test animals (6).

The branched chain amino acids (isoleucine, leucine and valine) are used specifically for protein synthesis and comprise up to 35% of muscle proteins, as well as play a role in neurotransmitter metabolism via competition for uptake mechanisms in the brain (7). Chronic deficiency of isoleucine may be manifested as a loss of muscle mass or as the inability to build muscle mass (5). Leucine plays a significant role in the prevention of muscle breakdown and has been shown to stimulate new muscle growth (5) and accelerate muscle repair (8).

Glutamic acid, an excitatory neurotransmitter, was found to be deficient as was phenylalanine, a precursor to tyrosine, epinephrine and nor epinephrine. Low phenylalanine levels can result in learning and memory difficulties, fatigue, autonomic dysfunctions, as well as depression and hypothyroidism (9). Low histidine levels have been

clinically associated with rheumatoid arthritis (10).

Methionine is also involved in neurotransmitter synthesis, specifically acetylcholine. Methionine is important in the detoxification of xenobiotics and free radical scavenging (11). A deficiency in methionine has been associated with chronic fatigue syndrome (11). A product of methionine, cysteine, is a component of glutathione, itself an essential component in detoxification and reducing lipid peroxidation. Adequate metabolism of the sulfur-amino acids is essential for the development of all the connective tissue proteins and for antibody production (12). Taurine, another product of methionine, plays an important nutritional role in the development of the nervous system (13), as well as in protecting cell membranes via attenuating toxic substances (14). Deficiencies in taurine have been clinically associated with neurological dysfunctions (15).

The laboratory results provided a rationale, or possible explanation of the mechanism by which some of the phenotypic characteristics often associated with this syndrome can manifest. As obvious deficiencies existed, supplementation was implemented. Neuromyopathy in children has been associated with vitamin E deficiency (16); thus, vitamin E supplementation was begun in November at a dose of 400 i.u. per day. A 1992 study reported use of vitamin E as being protective in cases of elevated peroxides and having the ability to reduce the symptoms of toxicity from xenobiotic exposure (17,18). A specific amino acid blend was acquired and started in December. Almost immediately, J.V. started to gain weight and develop physically and mentally. His parents reported significant improvements in his neurologic development. He quickly gained the ability to focus his attention. He became more responsive and less aloof to sounds, light and voice commands. His ability to resolve simple problems and to understand how things operate improved. Physically, muscle development initiated. Growth, in just a few months, accelerated beyond what had previously been seen in a period almost twice as long (see Figures 1 and 2). Growth rates in young children are normally quite variable. In J.V.'s case however, consistent gains in height, weight and development were observed only when supplementation was being utilized.

GROWTH IN WEIGHT: ACTUAL COMPARED TO NCHS MEDIAN WEIGHT. PERIOD: BIRTH TO 22 MONTHS

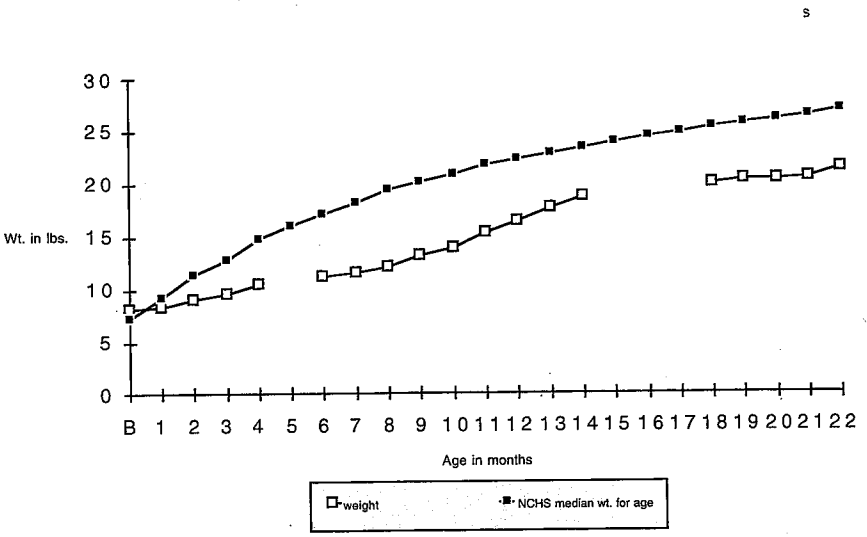


FIGURE 1

Median growth in weight for the periods when J.V. was off supplementation was just 5.66 oz per month. (During months one to eight, his weight gain was 3 lbs., 14 oz. For months 18-21, a gain of .44 lbs. was observed, totaling a 4 lbs., 5 oz gain during the 12 months without supplementation or 5.66 oz/month). Weight gain during the period with supplementation was 6 lbs., 11 oz in six months or 17.83 oz per month. Growth in J.V.'s length during the period from months one to five (without supplementation) totaled 1.25 inches. For months 18-21 (without supplementation), a total of .25 inches was observed. Total growth in length during the period (when measurement is known) without supplementation was 1.5 inches, or an average monthly growth of .167 inches. Growth in length during the period from months nine to 14 (using supplements) and again for month 22 (resumed supplements) totaled 2.25 inches or a monthly average of .321 inches. Despite these impressive data, J.V.'s parents informed me the medical geneticist who had diagnosed their son saw no advantage to using supplementation in a case of genetic deletion

GROWTH IN LENGTH: ACTUAL COMPARED TO NCHS MEDIAN. PERIOD: BIRTH TO 22 MONTHS

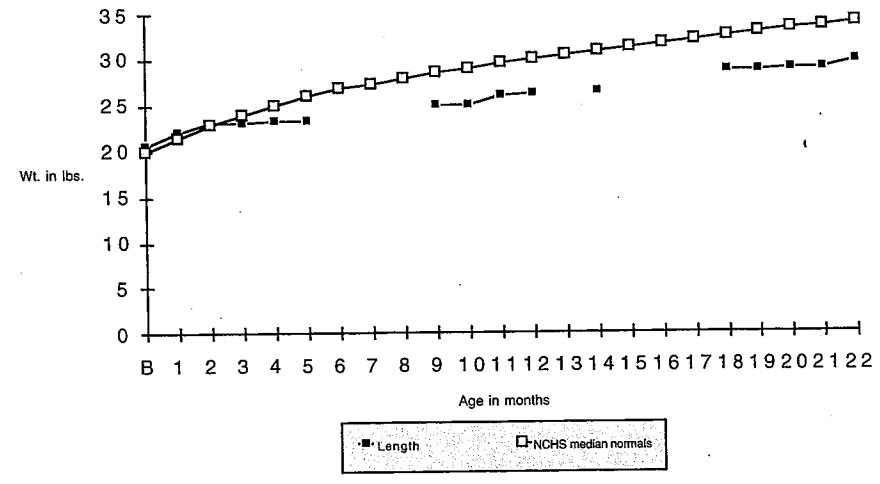


FIGURE 2

AMINO ACID ANALYSIS—SECOND

ESSENTIAL AMINO ACIDS			
Arginine	59 nmol/l		35-160
Histidine	81		70-140
Isoleucine	32	L	50-160
Leucine	71	L	90-200
Lysine	105	L	150-300
Methionine	18	L	20-50
Phenylalanine	36	L	55-140
Threonine	87	L	100-250
Tryptophan	50		20-60
Valine	137	L	150-420
ESSENTIAL AMINO ACID DERIVATIVES			
Gamma-aminobutyric Acid	1		< 5
Glycine	233		200-450
Serine	137		100-210
Taurine	105		50-250
Tyrosine	50		50-120
AMMONIA/ENERGY METABOLISM			
a-Aminoadipic Acid	3		< or = 4
Asparagine	57		45-130
Aspartic Acid	8		7-30
Citruline	21		15-70
Glutamic Acid	80		45-150
Glutamine	553		550-1050
Ornithine	51		50-200
SULFUR METABOLISM			
Cystine	25		10-90
Cystathione	3		< or = 5
Homocystine	<1		< or = 1
ADDITIONAL METABOLITES			
a-Amino-N-Butyric Acid	10		10-40
Alanine	190	L	300-600
Anserine	< 1		< or = 1
B-Alanine	< 1		< or = 5
B-Aminoisobutyric Acid	< 1		< or = 2
Carnosine	< 1		< or = 1
Ethanolamine	5		< or = 10
Hydroxylysine	< 1		< or = 1
Hydroxyproline	27		< or = 45
1-Methylhistidine	< 1		< or = 20
3-Methylhistidine	5		< or = 5
Phosphoethanolamine	51		< or = 75
Phosphoserine	12	H	< or = 10
Proline	116	L	130-400
Sarcosine	20	H	< or = 3

TABLE 2

and advised them "they were wasting their money". When the supplements were discontinued (months 18-21), J.V.'s growth both in weight and length arrested. (Note: Just prior to this writing, J.V. was again placed on supplementation. He has gained 12 oz and 3/4 inches in the first month since resuming the amino acids and vitamin E supplements (month 22). He gained just 2 oz in the previous three months, after having stopped amino acids & vitamins in September 1996. See sidebar letter from his parents for their observations of his status.)

Additional laboratory analysis was performed in January 1997. Tests included a repeat amino acid analysis and serum lipid peroxide, an organic acid (urine) analysis, antioxidant profile and erythrocyte fatty acid analysis. Despite the fact that J.V. had been off supplements for three months prior to his laboratory testing, considerably fewer amino acids were abnormally low (see Table 2). His lipid peroxide level remained elevated at 6.2nmol/ml and his glutathione level was found to be low at 29 mg/dl. Serum vitamin A and vitamin E levels were both low. His fatty acid profile revealed deficiencies in his gamma linolenic acid levels and eicosapentaenoic, docosapentaenoic and docosahexaenoic acid levels. A broader nutrient program is currently being implemented for J.V. and it is hoped that his growth and development will continue. It is unlikely that supplementation will correct this disorder; however, based on these results, it appears to possibly help limit the degree of genetic expression which may result as a consequence of the disorder.

While it is unknown why J.V. has improved from utilizing supplements, this case has demonstrated a clinical rationale for their use. Continued monitoring of this case over the next several years should provide more detailed information as to the efficacy of specific nutrient supplementation in cases of this type. For the moment, however, it appears that as there are no allopathic medical options for the resolution of this syndrome and as statistically, physical and mental development is deficient in almost all reported cases, the use of specific nutrient supplementation should be considered. Further scientific evaluation as to the nature of the metabolic abnormalities and deficiencies resulting from the autosomal deletion would be both enlightening and clinically significant as specific nutrient supplementation may reduce or render less significant the normal characteristics, or genetic expression, both physically and neurologically of children suffering certain genetic abnormalities.

REFERENCES

1. Smith's Recognizable Patterns of Human Malformation, 4th Edition. Edited by Kenneth Jones, W. Saunders, Phil. PA 1988 referencing; de Grouchy, et al, "Dysmorphic complexe avec oligo-

phrenic Deletion des bras courts d'un chromosome 17, 18. C. R. Acad. Sci.(D) (Paris), 256:1028, 1963.

2. Personal communication. The Chromosome 18 Registry & Research Society, San Antonio, TX, 1995.
3. "The Deletion Syndromes of Chromosome 18", The Chromosome 18 Registry & Research Society, San Antonio, TX. 1991.
4. Smith's Recognizable Patterns of Human Malformation, 4th Edition. Edited by Kenneth Jones, W. Saunders, Phil. PA 1988.
5. J. Alexander Bralley, PhD. "Clinical Relevance of Abnormal Amino Acid Values in Fasting Plasma" (Unpublished - MetaMetrix Medical Laboratory, Norcross, GA).
6. Furst, Peter, MD, PhD, "Dietary L-Lysine Supplementation: A Promising Nutritional Tool in the Prophylaxis and Treatment of Osteoporosis", Nutrition, Jan/Feb 1993; 9(1):71-72.
7. "Metabolism and Clinical Implications of Branched Chain Amino Acids and Ketoacids". Walser & Williamson, Eds. (Reference obtained from #5 above; no date or publisher could be provided.)
8. Fitzgerald, M. "Sports Medicine Expert Dispels Myths of Performance Enhancers: Diet Better Source of Building Blocks Than Supplements", The D.O., August 1992; 59-62.
9. Wurtman & Wurtman. Nutrition and the Brain, Vol. 1-4, Raven Press, New York, 1977-83.
10. Gerber, D.A. "Low free serum histidine concentration in rheumatoid arthritis.. A measure of disease activity", J. Clin. Invest. 55:1164-73, 1975.
11. Eaton, K.K. and Hunnisett, A. "Abnormalities in Essential Amino Acids in Patients with Chronic Fatigue Syndrome", Journal of Nutritional Medicine, 1991;2:369-375.
12. Scriver, C., Rosenberg, L. "Amino Acid Metabolism and its Disorders", Saunders, Philadelphia, 1973.
13. Sturman, J. "Taurine in Development", Journal of Nutrition, 118(10):1169-76, 1988.
14. Gaull, G. "Taurine in Pediatric Nutrition: Review and Update", Pediatrics, 83(3):433-42, 1989.
15. Huxtable and Pasanter-Moralies, "Taurine in Nutrition and Neurology", Plenum, 1982.
16. Kohlschutter,A. "Vitamin E and Neurological Problems in Childhood: A Curable Neurodegenerative Process", Developmental Medicine and Child Neurology, 1993;35:642-646.
17. Vatassery, G. "Neurochemistry of Vitamin E and Its Implications to Neurological Diseases," Beyond Deficiency:New Views on the Functions and Health Effects of Vitamins, New York Academy of Sciences, February 9-12, 1992.
18. Bakker, H.D. et al. "Vitamin E in a Mitochondrial Myopathy With Proliferating Mitochondria", The Lancet, July 1993; 342:175-176.

BIBLIOGRAPHY

de Grouchy, The 18p-, 18q- and 18r syndromes. Birth Defects O.A.S. 5:74-87, 1969

Faust, J., Habedank, M., Nieuwenhuijsen, C., The 18p- syndrome. Eur J Pediatr 123:59-66, 1976.

Fischer, P., et al, Autosomal deletion syndrome 46,XX, 18p-: A new case report with absence of IgA in serum. J. Med Genet 7:91-98, 1970.

Gorlin, R., Yunis, J., Anderson, V., Short arm deletion of chromosome 18 in Cebocephaly. Amer J Dis Child 115:473-476, 1968.

Leisti, J., et al, Absence of IgA and growth hormone deficiency associated with short arm deletion of chromosome 18. Arch Dis Child 48:320-322, 1973.

Ruvalcaba, R., Thuline H., IgA absence associated with short arm deletion of chromosome No. 18. J Pediatr 74:964-965, 1969.

Schinzel, A., Schmid, U., Lüscher, U., Nater, M., Brook, C., Steinmann, B., The 18p-syndrome. Archiv Für Genetik, 47:1, 1974.

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July 8, 1997

Dear Dr. Wallace,

I was privileged to attend the conference of the Chromosome 18 Registry and Research Society in Chicago on June 12, 1997. I was pleased to meet other families with children who have the same type of chromosomal abnormalities. A time was allotted for testimonials and I was privileged to stand up and relate some of our experiences with (J.V.) before 80-100 people. As I related our experiences (his lack of growth & development, his listlessness as a baby, his pleasant personality, the fact that there is little known about this in the medical community, etc.) most of the parents heads nodded understandingly. Their children had behaved the same way.

My objective in relating our experiences was to give hope to other parents. The nodding heads became interested faces, astonished at the fact of (J.V.'s) growth and improvement when we added nutritional supplements to his diet. After answering a few questions, the session was over. Probably at least 15, maybe 20 people came to me afterwards asking for more information: who is our doctor?, what supplements and lab did we use?. I photocopied a letter I had sent to the C18R&RS when we joined (and submitted information about (J.V.'s) medical records etc.) and gave it to interested parents. I also showed them the "before & after" pictures I had. People were astonished and I hope will pursue similar nutritional avenues for their children.

It seemed to me (and there are differing degrees of this abnormality I am sure), that (J.V.) was one of the healthiest children at the conference. I didn't see all of the children, but one little girl, who is about four months younger than (J.V.) was very small and certainly not the vibrant picture of youth that (J.V.) has become. She has been labeled a "failure to thrive" child and seeing her made me very grateful for (J.V.'s) progress. Others certainly looked by their facial features like they were not normal. (J.V.) is looking more and more like a normal child as time passes, even though he is still small for his age and not as far along developmentally as other children of a similar age. As long as we compare (J.V.) today with (J.V.) last month, we can see improvements. The physical therapist says that since he can walk (started at two years, two months), can squat to pick up a toy from a standing position and can stand up without holding on to anything for support, he is developmentally at *(approximately)* 15 months. Verbally and intellectually, he is at about two years and a couple of months....

I came away from the conference very grateful for our efforts (and the results) to help (J.V.) grow. Thank you for all you've done and we especially thank God for his intervention in our lives and (J.V.'s)....

Sincerely,

(name withheld)

BIOGRAPHY

Edward C. Wallace, DC, ND currently resides in West Branch, Iowa, and has been practicing for the past 14 years. Dr. Wallace graduated from National College of Naturopathic medicine in 1991 and Palmer College of Chiropractic in 1982. He includes Chinese medicine, nutrition, homeopathy and chiropractic in his practice. Dr. Wallace has published numerous articles in a variety of magazines and journals, and is a consultant for Frontier Herbs, based in Norway, Iowa.