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Treatment of Mood Lability and Explosive Rage with Minerals and Vitamins: Two Case Studies in Children

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ABSTRACT

A micronutrient supplement containing a broad range of dietary minerals and vitamins is being examined for the treatment of mood lability in both adults and children (Kaplan et al. 2001; Popper 2001). During pilot work, two medication-free boys with mood lability and explosive rage were studied in an open-label treatment followed by reversal and retreatment. One child was an 8-year-old with atypical obsessive-compulsive disorder, and the other was a 12-year-old with pervasive developmental delay. Both boys were monitored using the mood and temper items from the Conners Parent Rating Scale, as well as the Child Behavior Checklist. In addition, the boy with atypical obsessive-compulsive disorder was monitored with the child version of the Yale-Brown Obsessive Compulsive Scale. Both boys benefited from the micronutrient supplement when examined in ABAB designs: mood, angry outbursts, and obsessional symptoms improved when initially treated, returned when not taking the supplement, and remitted when the micronutrient supplement was reintroduced. Both boys have been followed and are stable on the nutritional supplement for over 2 years. These cases suggest that mood lability and explosive rage can, in some cases, be managed with a mixture of biologically active minerals and vitamins, without using lithium or other traditional psychopharmacologic agents.

INTRODUCTION

Over 70 years ago, researchers identified irritability and mood problems as being associated with vitamin deficiencies (Hoobler 1928), and clinicians reported positive results of treating mental illness with various essential trace minerals (English 1929; Reed 1929). Lithium is of course the most salient example of a mineral that affects mood disorders, but there are other findings that have been relatively neglected over the years. A literature has gradually accumulated that supports the notion that specific dietary nutrients, especially essential minerals, influence mood and mood disorders (Werbach 1999).

Calcium imbalances have been found to influence mood. Hyperparathyroidism is associated with changes in anxiety, depression, and cognitive function (Linder et al. 1988; Okamoto

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Some of these results were presented at the April 2001 annual meeting of the Society for Pediatric Research.

et al. 1997), and abnormally low intracellular calcium levels have been documented in patients with bipolar disorder (Dubovsky et al. 1992, 1994). Zinc, as another example, is known to play an important role in brain function and mammalian brain development (Sandstead 1985; Sandstead et al. 2000), and relative zinc deficiency may also play a role in the expression of certain psychiatric conditions. Serum zinc levels were significantly lower in 48 adults with unipolar depression compared to 32 normal volunteers, and the severity of zinc deficiency correlated with the severity of the depressive symptoms (Maes et al. 1994, 1997). In another study, serum zinc levels were found to be lower in 43 children with attention deficit hyperactivity disorder (ADHD) than in controls (Toren et al. 1996). Lower zinc levels correlated with severity of aggressive behavior in 135 assaultive incarcerated males compared to controls (Walsh et al. 1997). Similarly, serious iron deficiency, though rare in North America, is associated with irritability and aggression (Benton and Donohoe 1999). Some additional examples are selenium (Benton and Cook 1990) and chromium (McLeod et al. 1999).

NUTRITIONAL INTERVENTIONS

Although strongly effective dietary interventions for human mood disorders have been elusive, some nutritional intervention studies for vitamins and minerals have shown positive benefits for mental function. For example, a 60-day randomized, double-blind, placebo-controlled study of 120 women found that thiamine at a moderately high dose of 50 mg daily (recommended daily allowance is 1.1 mg) resulted in improved cognitive function and task performance, such as reaction time (Benton et al. 1997). Another randomized, double-blind, placebo-controlled trial in 50 adults revealed a significant relation between selenium intake and improved mood, as evaluated on a self-report questionnaire (Benton and Cook 1991). In one study, improved behavior was reported in 14 boys with ADHD given iron at 5 mg/kg daily (recommended daily allowance is 18 mg/kg) (Penland et al. 1997). Also, among 18 boys with ADHD, a better response to stimulant medication was predicted by higher baseline hair zinc levels (Arnold et al. 1990). Later, the data from these same children were reanalyzed using hair, red cell, and urine zinc levels: the initial results showing that zinc levels predicted response to stimulant medication were confirmed (Arnold et al. 2000).

Most nutritional research on micronutrients (i.e., vitamins and minerals) has examined the effects of a single nutrient, although there are some studies of complex formulations. A 1-year randomized, double-blind, placebo-controlled evaluation of a high daily dose of multivitamins (10 times the recommended daily dose) in 129 healthy young volunteers found that better mood was reported by those receiving the active treatment (Benton et al. 1995). Similarly, in a double-blind controlled trial in 740 well-nourished children in China given a broad-spectrum micronutrient formulation, improved task performance and physical growth were reported in a group also given zinc (Sandstead et al. 1998). There have also been a few reports of double-blind, placebo-controlled trials examining the effects of micronutrients on quality of life and psychological well-being. For example, Schlebusch et al. (2000) found that subjects in their micronutrient supplement group exhibited significant improvement on all psychometric measures of stress over the 30-day clinical trial, compared to subjects in the placebo group. Results of another clinical trial showed that, compared to placebo, treatment with a multivitamin and mineral supplement that included calcium, magnesium, and zinc were associated with significant decreases in anxiety and perceived stress in healthy, normal volunteers (Carroll et al. 2000).

In general, the strategy of studying several nutrients together is unusual, especially given the standard scientific approach of examining the effects of one pharmacologic agent at a time. In our research, the decision to examine a supplement containing multiple nutrients was initially derived from observations in agriculture. Aggressive behavior in farm animals presents a major cause of lost revenue to agribusiness, and various approaches have evolved based on animal nutritional science for managing this problem. In some regions, aggressive farm animals are treated with a

mixture of nutrient ingredients, consisting primarily of trace elements (minerals). A comparable formulation recently became available for human use and is the intervention currently under investigation: it consists primarily of minerals (but not lithium), vitamins, and antioxidants.

Based on the animal findings, and subsequently on the anecdotal reports of its use in humans provided by the developers of this formulation, David Hardy and Anthony Stephan, we began conducting systematic open-label case series of the micronutrient supplement for treating bipolar disorder in adults and mood problems in children. (Information about this supplement can be found on the company's Website, at www.truehope. com. None of the investigators is financially involved with the company.) In an unselected case series of 14 adults with bipolar disorder, the micronutrient supplement resulted in clinically and statistically significant improvements, as measured by the Hamilton Depression Scale, the Brief Psychiatric Rating Scale, and the Young Mania Rating Scale (Kaplan et al. 2001). The effect size of the intervention was large (>0.80) for each outcome measure, and symptom reduction ranged from 55–66%. In addition, the need for psychotropic medication decreased by more than 50% in this sample. Similarly, in an unselected case series of nine children with mood and behavior problems, the effect of the same nutrient supplement was monitored for a minimum of 8 weeks of treatment (Kaplan et al. submitted). Outcomes were measured with the Child Behavior Checklist (CBCL; Achenbach 1991), the Youth Outcome Questionnaire, and the Young Mania Rating Scale. Again, the supplement was clinically beneficial for this sample and the effect size for all outcome measures was large (>0.80).

During some of our open-label pilot work, two families expressed concern that they were unable to assess the effects of the intervention supplement because of concurrent environmental changes. In both cases, the families decided to stop the micronutrient supplement to see whether clinical regression occurred but agreed to continue monitoring the mood and behavior of their children during the treatment withdrawal. We present here the two open-label case studies of children with mood swings and explosive rage who were studied in an ABAB format. This report describes the first cases involving some element of experimental control, specifically using the clinical-controls methodology of reversal and retreatment.

METHODS

Children were recruited for the pilot work by notifying local pediatricians and child psychiatrists in a large urban tertiary care pediatric hospital about the research. It was explained that the study would examine a nutritional intervention that might be acceptable to families who refused standard medication treatment. The fact that this experimental intervention consisted of dietary nutrients appealed to families who felt uncomfortable using psychiatric medication or had previously experienced adverse medication effects. These two cases were studied as part of the pilot work that eventually led to the formal open-label case series reported elsewhere (Kaplan et al. submitted); hence, the protocol was not as formal and there were few inclusion or exclusion criteria. To participate, the child simply had to exhibit mood lability, irritability, uncontrollable temper outbursts, or aggression; had to be at least 8 years old and comfortable swallowing large capsules; and had to be otherwise physically healthy. The available safety and toxicity data were provided to each family, and the rationale for the research was presented. Families were reminded of standard pharmacologic treatments for their children, and in one of the two cases presented here the child had already tried several psychiatric medications. This protocol was reviewed and approved by the Conjoint Health Research Ethics Board of the University of Calgary's Faculty of Medicine. Parents signed consent forms prior to participating in the trial, and children provided their assent in writing.

The intervention consisted of the micronutrient supplement called E.M.Power+, manufactured and distributed by Evince International (Farmington, Utah). It contains 36 ingredients, 33 of which are relatively high levels of ordinary dietary constituents (see Table 1). Pilot

work had revealed that adverse effects of the micronutrient supplement were minimal, consisting of nausea (usually transient) and occasionally loose stools. The full dosage consists of 32 gelatin capsules daily, which were distributed as 8 capsules taken four times daily, with a minimum of 2 hours between dosages. In general, the large number was announced to children only after ascertaining how many capsules they thought they could swallow each day (the number usually being around 75–100, based on their expressed belief that they could swallow one every 10 minutes for all their waking hours). This strategy was employed to minimize the number of capsules actually required, compared to what the children themselves voiced as being within their capacity. The children were also told that the large number of capsules was due to the bulkiness of minerals, as illustrated by the size of rocks and mountains, which are composed of minerals.

Toxicity of these ingredients is believed unlikely to be a problem. The individual ingredients of the supplement are all below the amounts that are known to be potentially toxic in healthy children and adults (Strain and Caballero 1999). In addition, previously completed pilot work in a group of 12 children revealed that heart rates, blood pressure, and blood samples remained normal over

TABLE 1. INGREDIENTS OF E.M.POWER+

	32 Capsules	*8 Capsules*	*RDA for children ≥4 years*
Vitamin A (as retinyl palmitate)	9,600 IU	2,400 IU	5,000 IU
Vitamin C (as ascorbic acid)	1,000 mg	250 mg	60 mg
Vitamin D (as cholecalciferol)	1,600 IU	400 IU	400 IU
Vitamin E (as d-alpha tocopheryl succinate)	400 IU	100 IU	30 IU
Vitamin B1 (as thiamine mononitrate)	20 mg	5 mg	1.5 mg
Vitamin B2 (as riboflavin)	22 mg	5.5 mg	1.7 mg
Vitamin B3 (as niacinamide)	100 mg	25 mg	20 mg
Vitamin B6 (as pyridoxine hydrochloride)	28 mg	7 mg	2.0 mg
Vitamin B9 (as folic acid)	1,600 μg	400 μg	400 μg
Vitamin B12 (as cyanocobalamin)	1,000 μg	250 μg	6.0 μg
Biotin	100 μg	25 μg	10 μg
Pantothenic acid (as d-calcium pantothenate)	24 mg	6 mg	10 mg
Calcium (as calcium complex,[a] calcium amino acid chelate)	2,200 mg	550 mg	1 g
Iron (as iron amino acid chelate, iron complex[a])	24 mg	6 mg	18 mg
Phosphorous (phosphorous complex[a])	1,400 mg	350 mg	1 g
Iodine (from kelp)	300 μg	75 μg	150 μg
Magnesium (as magnesium amino acid chelate, magnesium complex[a])	1,000 mg	250 mg	400 mg
Zinc (as zinc amino acid chelate, zinc complex[a])	80 mg	20 mg	10–15 mg
Selenium (as selenium amino acid chelate, selenium complex[a])	400 μg	100 μg	None
Copper (as copper amino acid chelate, copper complex[a])	12 mg	3 mg	2.0 mg
Manganese (as manganese amino acid chelate, manganese complex[a])	16 mg	4 mg	None
Chromium (as chromium amino acid chelate, chromium complex[a])	1,000 μg	250 μg	None
Molybdenum (as molybdenum amino acid chelate, molybdenum complex[a])	264 μg	66 μg	None
Potassium (as potassium complex[a])	400 mg	100 mg	None

Note: Treatment began with 32 capsules/day; maintenance dose was 8 capsules/day.

There is currently a proprietary blend, for which daily values are not established: dl-phenylalanine, glutamine (as l-glutamine), citrus bioflavonoids (from peel), grape seed (*Vitis vinitera*), choline (as choline bitartrate), inositol, Ginkgo biloba (from leaf), methionine (as l-methionine), germanium (as *Germanium sesquioxide*), boron (as boron amino acid chelate), vanadium (as vanadium amino acid chelate, vanadium complex[a]), and nickel (as nickel amino acid chelate, nickel complex[a]). Other ingredients include gelatin, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Manufactured for The Synergy Group of Canada, by Evince International, Farmington, Utah. RDA = recommended daily allowance.

[a]Saccharide complex.

16 weeks (unpublished data, Kaplan and Fisher 1998). Also, there was no evidence of vitamin or mineral toxicity, such as weight loss, muscle weakness, nausea, vomiting, or anorexia in these children.

Although structured diagnostic interviews were not used for the two children presented here, their clinical diagnoses were made by the child's psychiatrist (case 1) and developmental pediatrician (case 2) based on several years of clinical experience with the child, including treatment and monitoring. Over the years, physical examinations by the children's physicians revealed no abnormalities, and routine laboratory testing including thyroid evaluation yielded no significant findings.

To be able to assess symptom change, parents evaluated their child's behavior daily using a modified Conners Parent Rating Scale (CPRS; Conners 1991). Each item on the CPRS was scored in the routine way, on a scale of 0 to 3 (0 = *not at all,* 1 = *just a little,* 2 = *pretty much,* 3 = *very much*). The two items on the CPRS that were targeted as primary outcome measures for each child were (a) mood changes quickly and drastically and (b) temper outbursts, explosive, unpredictable behavior. At least 1 week of baseline monitoring by the parent using the CPRS preceded the introduction of the micronutrient supplement.

CASE 1

An 8-year-old boy diagnosed with atypical OCD, ADHD, mood lability, and explosive rage was referred by his psychiatrist (BG) (see Figs. 1 and 2). Although his obsessions were severe and pervasive, he displayed no discernible compulsions; for this reason his OCD was considered to be atypical. Tantrum behavior had been a problem since age 6, and he was reportedly having significant angry outbursts at least twice daily for the prior year. During one period of monitoring, his parents counted six "blowups" in a single hour. He exhibited a variety of other symptoms, including depressive withdrawal, irritability, anxiety, hyperactivity, and hypertalkativeness. His primary obsession symptom was an intense and pervasive preoccupation with guns and knives; weapons intruded repeatedly into his spontaneous conversation and his play. In addition, he sometimes expressed an intense fear that wild animals would come crashing through their roof at night from the large park adjacent to their home. Suicidal ideation or comments were not apparent, but his teachers expressed concern about his depressive withdrawal in class. At the time of referral, his rage attacks had begun to include physical aggression against relatives and friends, and his family

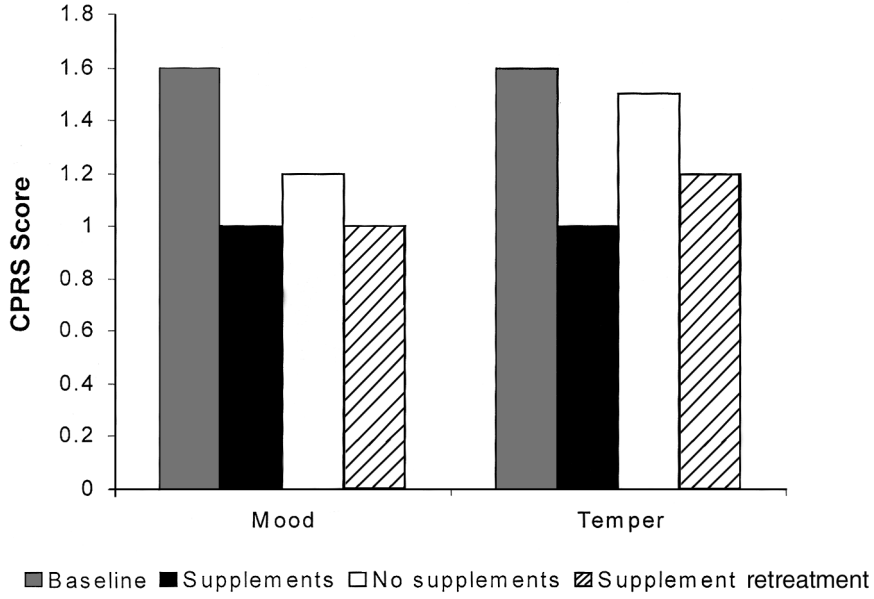

FIG. 1. Case 1: mean mood and temper scores from the Conners Parent Rating Scale (CPRS).

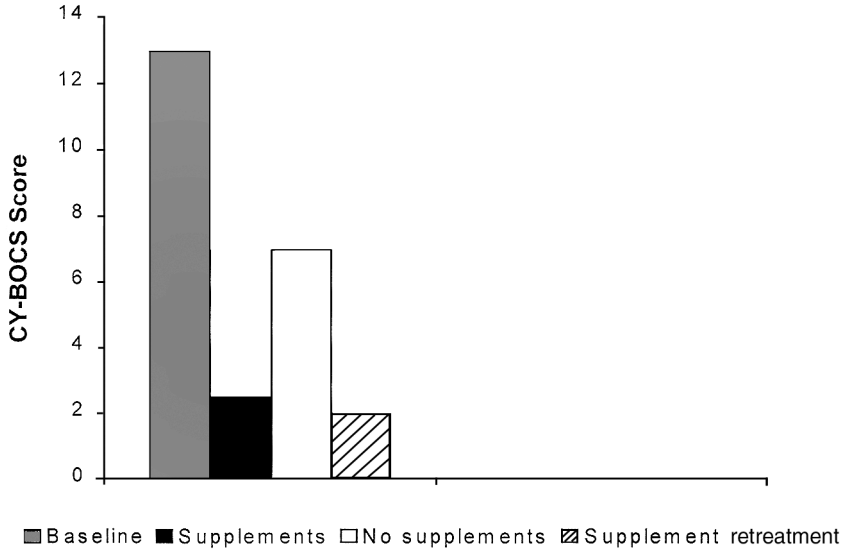

FIG. 2. Case 1: scores on the Children's Version Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

reported living in fear of his potential for violence. There were no explicit psychotic symptoms, and during each interview this child seemed to have a clear sense of reality and intact reality testing. Also, he definitely recognized that his obsessions were not normal, and he wished to be free of them.

The parents reported that the child was happy and affectionate until the age of 4 years, after which he became progressively more irritable, angry, withdrawn, and increasingly obsessed with guns. No traumatic or significant event at age 4 was reported by parents or child. Parents and teachers described the boy as controlling and bossy in social situations. When assessed by the school psychologist at age 7, reports of parents and teachers were consistent and suggested that he had ADHD and depressive mood. He was reported to have periods of being quite withdrawn in school, but he also experienced occasional emotional outbursts in his interactions with other children. In general, he was seen as a child with significant anger management problems as well as a social skills deficit.

Since age 7, the child had been seen regularly by a psychologist, with a treatment focus on anger management and social skills. A trial of methylphenidate was terminated by his psychiatrist within a month because it seemed to exacerbate his mood symptoms. He had not been taking any psychiatric medication for 2 years prior to the time of referral. Although the parents were open to psychopharmacologic treatment, they were more interested in trying a nutritional approach.

The mother had a history of mild and apparently unipolar depression, for which she was taking an antidepressant. No other family psychiatric history was elicited, including OCD, mood disorders, violence, suicide, and anxiety. Both parents were described as calm individuals who reportedly rarely raised their voice or threatened the children or each other. The patient's 4-year-old sister was reported by the parents to raise no mood or behavioral concerns.

Baseline

At the first interview, the child was explicit and expressed awareness of his obsession with guns, announcing "Yeah, I can't get them out of my head." The obsessions were clearly egodystonic, and he indicated that he was motivated to try anything that would remove these obsessive thoughts. Behaviors consistent with ADHD and OCD were apparent, but there was no evidence of tics. Mood was labile. The CBCL (Achenbach 1991) revealed significant behavioral difficulties, with *T* scores above the clinical cutoff of 70 (a *T* score of 70 is 2 SD above the normative mean) on seven of the eight scales: only delinquent behavior was not significantly ele-

vated (T = 63), as expected in a child so young. At baseline, the mean score on the CPRS mood lability item was 1.6, and on the tantrums item was also 1.6; as stated above, each item ranges from 0–3. On the obsessions portion of the Child Version of the Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al. 1997), his baseline score was 13; the compulsions section was not used because the child displayed none.

First intervention with micronutrient supplement

The child began the supplement at the full dose of 32 capsules, taken as 8 capsules four times daily. No gastrointestinal discomfort or other adverse effects were reported. He was remarkably compliant with taking the large number of capsules, and expressed his awareness that his compliance was being requested specifically to determine whether the capsules would help with the unpleasant thoughts that were troubling him.

By day 15 of micronutrient treatment, the family reported a reduction in the frequency and especially the duration of rage attacks. He was noted to have a generally calmer mood. Although there was no spontaneous parental or self-report of a change in the obsession with weapons, his CY-BOCS score had decreased from 13 to 9.

Two weeks later, his parents reported that he was again having behavioral difficulties, both at home and at school. They attributed this increase in symptoms to the fact that he had been told about a decision to move him to a different school, a specialized setting for children with behavior problems. His reaction to the impending move was anxiety and increased emotional lability. His CY-BOCS increased to 13. He did, in fact, change schools at the end of treatment week 6.

By the end of treatment week 9, the parents reported a decrease in obsessions; the child confirmed this, saying that he did not "have time to think about guns anymore." His CY-BOCS score reduced to 5.

By the end of week 12, the tantrums, general moods, and obsessive symptoms were all reported to have improved to some extent, according to parents and child.

By the end of week 16, the parents were reporting no significant residual symptoms, and the mother felt that he was "wonderful." The child reported that he was able to go all day without thinking about guns. All CBCL scale scores were below 70, and his CY-BOCS score was 2. The Withdrawn scale of the CBCL decreased from 73 at baseline to 54 at the end of week 16, Somatic Complaints decreased from 75 to 50, Anxious/Depressed decreased from 91 to 61, Social Problems decreased from 80 to 64, Thought Problems from 73 to 57, Attention Problems from 75 to 60, Delinquent Behavior from 63 to 50, and Aggressive Behavior from 85 to 60. His average score for the mood lability item of the CPRS decreased to 1, as had the average score for temper outbursts (cf. Figs. 1 and 2). Scores of 1 on the CPRS correspond to the child having the behavior "just a little."

Treatment withdrawal

After several weeks of stable symptom control, the parents and the investigators agreed that the clinical improvements were impressive but not clearly attributable to the micronutrient supplement, primarily because of the change in school placement 6 weeks into the trial. At their own initiative, the parents made a decision to stop the micronutrient supplement but agreed to continue the ongoing monitoring of the boy's behavior. During week 17 of the treatment, the supplement was discontinued; at that time, the CY-BOCS score was 4, and all CBCL scale scores were below clinical cutoffs.

The next evaluation session was conducted at the end of week 3 following discontinuation of the micronutrient supplement. At that time, the mother reported that he was generally doing well, with no significant deterioration in mood. On the other hand, both parents noted that his obsessive thoughts were returning, with a progressive daily increase in his interest in guns, and they feared a return to the baseline state.

At the end of 6 weeks of the discontinuation phase, the parents reported a significant clinical regression. The boy was described as obstinate, argumentative, loud, provocative, and constantly talking about guns. He was noncompliant in the home and easily lost his temper. His

parents strongly suspected that for the first time he was minimizing the report of many of his symptoms during interviews in order to avoid having to restart treatment; however, he introduced the topic of guns within 20 seconds of arriving for his appointment that day. Although the CY-BOCS score was only 7, he admitted to having significant intrusive thoughts but during the interview chose to emphasize repeatedly his ability to fight them, an ability that he recognized he had not had prior to taking the supplement. A repeat administration of the CBCL revealed that once again there were three scales exceeding clinical cutoffs (Anxious/Depressed = 77, Social Problems = 80, and Aggressive Behavior = 78). His scores on the CPRS also increased for mood lability and temper outbursts. The child seemed only minimally aware of the overall clinical regression, but he did recognize that his peer relationships were worsening. In view of the clinically apparent deterioration, the parents decided, in concert with the child and the clinician, to restart the micronutrient supplement.

Reintroduction of nutrient treatment

The child restarted the micronutrient supplement at the full dose of 32 capsules daily. At the evaluation session 2 weeks later, the parents reported that there was visible improvement in mood, temper, and obsessions. He was reported to be more "mellow" and more in control of his temper. His mother remarked that she had overheard him using a self-talk anger management strategy taught to him previously: she heard him say "Now watch your temper, count, count!" He was still playing with guns, but they did not seem all-consuming.

By 5.5 weeks back on nutrient treatment, the parents reported that the recovery time from blowups had decreased from 30 to 5 minutes. The child said, with a knowing laugh, "The pills slow my brain down so I can think before I decide to punch the guy's lights out." His CY-BOCS was 7.

Once back on the micronutrient supplement for 11 weeks, his CY-BOCS score was 2. By week 18, the school psychologist reported that behavior and attention had both improved sufficiently that he was ready to be reintegrated back to a regular school. His scores for mood lability and temper outbursts also dropped to the initial levels when the micronutrient supplement was first introduced (see Fig. 1).

At a final research follow-up assessment 1 year later, he was successfully proceeding with his education in a regular classroom. There were no behavioral or attentional difficulties reported, and his CY-BOCS was 1.

Second treatment withdrawal and reinstatement

Approximately 9 months after the last research interview, the family drifted away from using the micronutrient supplement and was no longer being monitored. The parents hoped that their son had matured sufficiently that the capsules would be unnecessary. However, they later telephoned us and reported that he had had a severe explosive rage attack about 4–5 weeks after stopping the supplement. In response, the family reinstated nutrient treatment, and he has maintained the micronutrient supplement since then. At a follow-up visit 8 months after that incident, the 11-year-old stated that he no longer "flips out," that he now has more friends, and that he is enjoying life. The parents reported an increase in self-confidence and maturity, and no evidence of the symptoms of the past. Neither the child nor the family reported any adverse treatment effects. After 26 months of treatment, the child continues to do well on a maintenance dose that is 25% of his initial full dose.

Case summary

This child was studied quantitatively in an ABAB design, which his parents independently extended to an ABABAB format. The overall sequence involved 2 weeks of baseline, 17 weeks of treatment, 6 weeks of withdrawal, and 5 weeks of treatment reintroduction. When not taking the supplement during baseline and during two withdrawal phases, he consistently showed irritability, explosive rage, and obsessional thoughts about guns. Taking the micronutrient supplement was associated with virtually complete remediation of his obsessional thoughts and significant improvements

in his mood lability. His overall demeanor became much calmer, and his temper was well controlled.

CASE 2

This 12-year-old boy was initially diagnosed at age 2 with autism and was rediagnosed at age 4 with pervasive developmental disorder with Asperger characteristics (see Figs. 3 and 4). He also exhibited severe ADHD, learning problems, an irritable temperament with mood problems, and explosive outbursts but had no history of tics. Although often difficult as a young child, the severity of symptoms increased significantly with puberty. He began to display a wider variety of significant behavioral and social problems, including emotional outbursts, runaways from home, and reporting his parents to the police. Irritability and unpredictable explosive behavior characterized the daily experience of this boy. There was no history of suicide attempts or psychotic symptoms. Asperger characteristics included an intense focus on a narrow range of interests, often accompanied by obsessional worries about "germs." He was also described as anxious, often worrying about school the next day. His overall attitude tended to be negative and pessimistic, which was associated with his worrying ahead of time about possible negative experiences he would have to endure the next day at school. Although his negative attitude, inattention, and social problems were considered problematic, the main concern was his explosive temper.

The family is very close and supportive, with all three older siblings playing an active role in helping raise this boy. Some siblings had mild attentional symptoms, but there was no modeling of explosive temper in this household. This boy has been monitored closely for his entire life by pediatricians, psychiatrists, and psychologists. His mother, a psychologist with a primary interest in children with special needs, was very capable at accessing the city's resources for therapy and special education.

Dextroamphetamine 15 mg daily, used for 16 months, was thought by his teachers to help him focus on his schoolwork, but his parents saw no benefit for his irritability and mood symptoms. With the support of the pediatrician, the parents chose to stop the dextroamphetamine 1 week prior to participating in this medication-free trial in order to address his explosive anger, irritability, obsessional worries, and negative attitude.

Baseline

When this child was referred to the study by his pediatrician (GF), his school situation had been deteriorating for several months. A full-time aide was no longer sufficient to enable him to remain in a public school, and his parents were looking for alternatives. His teachers described him as loud, angry, disruptive, rude,

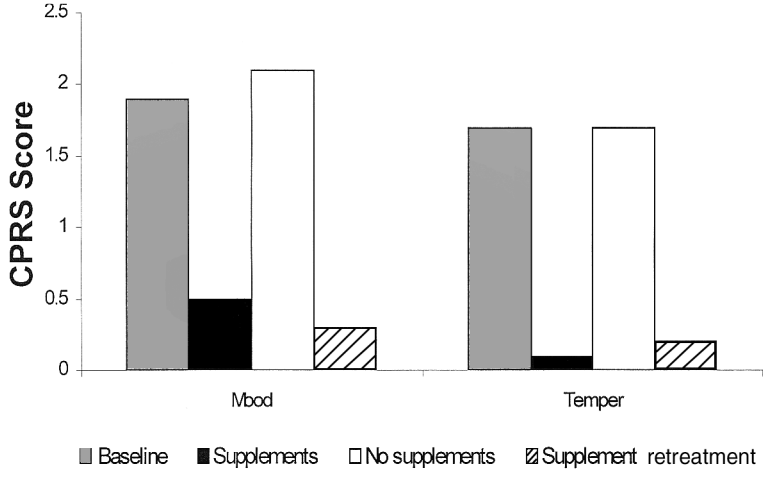

FIG. 3. Case 2: mean mood and temper scores from the Conners Parent Rating Scale (CPRS).

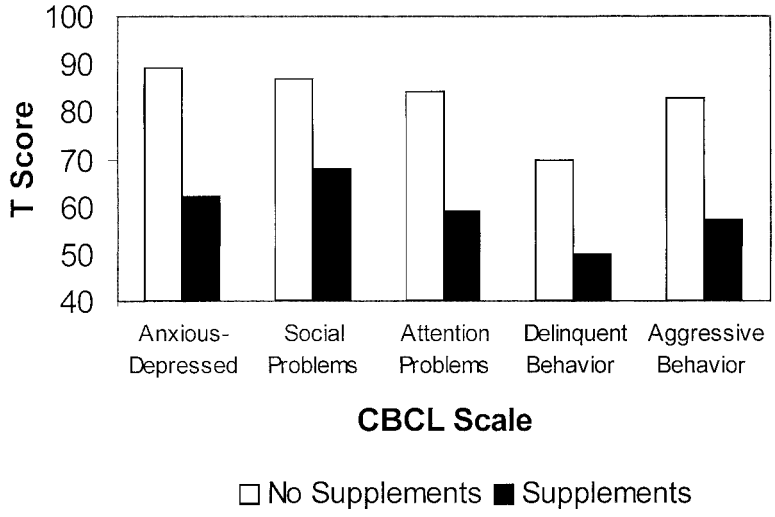

FIG. 4. Case 2: child Behavior Checklist scores (CBCL).

and unable to control his anger. His attitude was reported to be negative about everything, and he was described as being always irritable. Squabbles with playmates often continued for hours, and even a brief altercation would adversely color this child's entire day. At baseline, his mean CPRS score for mood lability was 1.9 and for temper outbursts was 1.7 on the scale from 0–3.

First intervention with micronutrient supplement

This 12-year-old was started on the micronutrient supplement at the full dose of 32 capsules daily. No adverse effects were encountered. After 3 weeks on the supplement, the parents reported that both mood and behavior were much improved, noting that his temper outbursts ceased much more quickly than previously. His parents described a marked lifting of his general mood, less negativity in his attitude, and a decrease in worries about germs. His mean scores on the CPRS decreased to 0.5 for mood lability and 0.1 for temper outbursts, indicating that mood and temper were close to the scale minimum of 0 (*not at all problematic*).

Although mood and behavior had apparently improved, his distractibility at school was a problem without stimulant medication. Six weeks after beginning the micronutrient supplement, stimulant medication was restarted at a dose of 5 mg methylphenidate twice daily (compared to 15 mg dextroamphetamine daily previously) and resulted in a very marked improvement in attention according to both parents and teachers.

Treatment withdrawal

After 15 weeks on the micronutrient supplement, the parents remained very pleased with the boy's emotional state and temper control. Although there were no noticeable adverse effects, over time the child found it difficult to take the large number of capsules each day. Also, the child moved from a regular public school to a private academy for children with learning and attention problems. Thus, partly due to the boy's difficulty with taking the large number of pills and partly due to his parents' uncertainty about whether his improvements might have been a result of his new school placement, the parents experimented with a gradual dose lowering over the following 6 months and then an eventual discontinuation of the micronutrient supplement. After almost 3 weeks without the supplement, his CPRS scores for mood lability and temper outbursts had increased back to baseline levels.

Reintroduction of micronutrient supplement

The parents, noting the contrast in his clinical condition without the micronutrient supplement, decided with the child to restart the

nutrient treatment. Stimulant medication continued throughout this time. Although a CBCL had not been employed during the first intervention, the parents were asked to add this questionnaire to enhance the information during the second period of supplement treatment. Prior to restarting the micronutrient supplement, a CBCL revealed elevated scores on all eight scales (all > 70). The family reported that this boy's irritable moods and negative attitude were once again the focus of family life, in that every event, no matter how small, triggered an emotional reaction from him. He also spent part of every evening worrying about school and interpersonal interactions.

After 6 weeks back on the micronutrient supplement, all of the eight CBCL scales had decreased to levels below clinical cutoff (70) (Fig. 3). The reductions in *T* scores from reversal to reintroduction for each scale of the CBCL were as follows: Withdrawn (73 to 58), Somatic Complaints (70 to 53), Anxious/Depressed (89 to 62), Social Problems (87 to 68), Thought Problems (70 to 57), Attention Problems (84 to 59), Delinquent Behavior (70 to 50), and Aggressive Behavior (83 to 57). Fig. 4 illustrates the changes in CBCL scale scores that reflected his most significant problems prior to treatment: anxiety, social problems, attention, and delinquent and aggressive behavior. Similarly, CPRS scores had reduced to 0.3 for mood lability and 0.2 for temper outbursts (see Fig. 3).

At follow-up, the child has been doing well emotionally after 32 months. He is currently taking 25% of his initial dose of the micronutrient supplement. At the beginning of the next school year, he returned to taking 15 mg dextroamphetamine (rather than methylphenidate) to help him focus during school days, suggesting that the supplement is not sufficient for his inattention, although it helped his mood problem. On the combination of dextroamphetamine and the micronutrient supplement, he has been doing well in school both academically and socially: his parents report that he works hard, studies conscientiously, copes with stresses comfortably, and is able to quickly resolve his feelings when conflicts arise. Most apparent to the family is his more positive attitude and controlled temper. He continues to experience no adverse effects from the supplement.

Case summary

This child's scores on the CPRS showed a clear clinical benefit from taking the micronutrient supplement, particularly in the area of mood stabilization. Also, the CBCL showed clear improvements when the supplement was reintroduced, with changes observed in all scales. The dose of stimulant medication at the end of the trial was the same 15 mg dextroamphetamine as he was taking prior to the micronutrient supplement. Hence, it appears that the nutrients added clinically useful improvements in mood and behavior, although they may not have significantly enhanced his attention. The overall sequence involved 1 week of baseline, 15 weeks of treatment, 3 weeks of withdrawal, and 6 weeks of treatment reintroduction.

DISCUSSION

Both children with mood lability and explosive rage showed clinically significant improvements while taking a nutrient supplement consisting of minerals and vitamins. In the first case, psychiatric medications were no longer needed. In the second case, a psychostimulant remained helpful for treating inattention. The clinical effectiveness of the nutrients was confirmed by treatment withdrawal and reinstatement (ABAB design), with routine outcome measures supporting changes in mood and behavior. There were no adverse effects of the micronutrient supplement noted by the two children or their parents. The main difficulty involved in these treatments was the large number of capsules required in the daily regimen, specifically 32 capsules during the initial "loading" period. However, long-term stabilization was achieved in each case on a lower maintenance dose, consisting of 8 capsules daily.

The rationale for doing reversals in each case involved changes in school placement during the course of the intervention. To assess whether symptom remission was due to the environmental change or to the micronutrient supple-

ment, the parents requested a trial of treatment withdrawal. In both cases, this situation allowed the demonstration that mood lability increased when the micronutrient supplement was removed and was ameliorated when it was reintroduced, thereby strengthening the evidence for the role of the supplement in the observed mood stabilization.

There were some rather strong similarities in the types of symptoms that changed in both cases. For both boys, supplementation resulted in fewer emotional outbursts, better temper control, and more positive mood. Both families spontaneously reported that one of the first signs of improvement was a decrease in the duration of temper outbursts, followed later by a decrease in frequency. In addition, both boys had anxious obsessional types of thinking (case 1 about guns and knives, case 2 about germs), although neither was a classic case of OCD. For both boys, the micronutrient supplement ameliorated the obsessional thinking. Two other similarities between the two cases are worthy of note: both boys showed mood stabilization, and neither boy experienced any adverse effects of taking this nutritional supplement. Whether or not inattention was improved in case 1 is not known: the focus of everyone's concern for this boy was his potential for violence mixed with his obsession with guns. In case 2, there was no apparent improvement in the boy's attentional problems and no difficulty in mixing the supplement with a low dose of stimulant medication.

Limitations

Open-label trials are inherently subject to expectancy effects and observer bias. In both these cases, blinding was not possible, and the allocation of treatment order was, of necessity, not random. For both children, the primary observers and raters were the parents, who knew when the children were taking the nutrient treatment and when they were not. Even a reversal design cannot eliminate the impact of the potential bias of unblind observers. However, the changes observed in both children were maintained for more than 2 years, which ought to be sufficient time for a positive expectancy bias to habituate. Also, the significant improvement in the CY-BOCS score for case 1 is less likely to be influenced by parental bias: the CY-BOCS was employed as a structured interview with the child, carried out in a private room to minimize parental influence.

Structured diagnostic interviews were not carried out in this preliminary work, and so the diagnostic picture of each case may not be entirely complete. The clinical descriptions of symptom complexes and behavioral problems are, however, relatively rich, as each patient had a long history with his referring physician. It should be mentioned that bipolar disorder is rarely diagnosed in children in this city, whereas elsewhere both children might have been candidates for that diagnosis.

Swallowing a large number of capsules is a considerable obstacle for many children. Compliance was not difficult for case 1 but was a source of considerable family stress for case 2. When the initial loading dose was gradually decreased by the families to the 25% maintenance dose, compliance was less of a challenge. More palatable versions of the micronutrient supplement, including a powder to be mixed in juice, are currently being developed by the manufacturer to lessen this problem.

In both cases, the improvements associated with the nutrient treatment were clinically significant but were not evidence of complete normalization of brain function or behavior. Case 1 still appears to have a significant social-skills deficit, resulting in some continued peer problems. Case 2 still has Asperger's syndrome, learning problems, and attentional symptoms requiring independent treatment. Perhaps it should be emphasized that the results from these two case studies do not shed any meaningful light on whether this micronutrient supplement has potential therapeutic benefit for the treatment of ADHD. Case 2's results suggest that it may not benefit the hallmark symptom of inattention, but research designed explicitly to evaluate this topic is needed.

Safety

Although these two boys did not experience any adverse effects, observations in other chil-

dren and adults indicate that adverse effects can occur, albeit relatively minimal ones (Kaplan et al. 2001; Popper 2001). Nausea has been reported in some individuals, but it appears to be less likely if the capsules are consistently taken with food, and also if the dose is increased slowly. Some individuals have described loose stools, but only a few have reported diarrhea or other gastrointestinal symptoms. Adverse effects, when present, have been mild and transient, although a few patients have needed to lower the dose of micronutrient supplement. Discontinuation of the nutrients has been required only in rare cases, generally when gastrointestinal problems were preexisting and prominent.

The safety of this formula has been supported by nutrition and biochemical consultants and reviewers, but there are still safety and toxicity issues that remain to be addressed. In the heart rate, blood pressure, and blood sample data collected during pilot work and mentioned above (unpublished data, Kaplan and Fisher 1998), all children remained well and there were no health concerns. On the other hand, the micronutrient supplement has not been studied systematically for safety and adverse effects in normal volunteers. In addition, a multi-ingredient formulation could lend itself to unpredictable effects due to the interaction of the individual ingredients, and these need to be studied. Adverse effects data, renal function tests, and various other lab measures are being collected systematically in ongoing clinical trials.

The number of capsules required during the initial treatment is a considerable obstacle to using the supplement with young children. The two cases reported here are consistent with the clinical observations of a number of psychiatrists, who report that eventual dose reductions are possible (Popper 2001). The absence of insurance reimbursement for natural health products added to the families' motivation to minimize the dose ingested. The change from 32 capsules per day to 8 per day is a significant decrease but is not unusual for children who are currently taking this micronutrient supplement. Even so, swallowing 8 capsules per day is still an insurmountable obstacle for some children.

Open questions

This research joins the few studies that have demonstrated psychological effects following treatment with a complex nutrient formulation that includes vitamins and minerals (Benton 2001; Benton and Roberts 1988; Carroll et al. 2000). One question that emerges when evaluating research that employs a complex formula is, "Which of the many ingredients are relevant?" As discussed recently by Popper (2001), this question is worth pursuing only after there is formal proof of the efficacy of the formulation as a whole.

It is important to acknowledge that an intervention consisting of such a complex list of ingredients is unusual in the area of human health. Virtually all studies on medication treatments, and even much of the research on nutritional interventions, focus on a single ingredient or one single medication at a time. When two or more agents are examined together, as in cancer chemotherapy, each agent has typically undergone careful individual evaluation. This perspective shapes virtually all scientific methodology and clinical practice; it is possible, however, that a broad-based multi-ingredient approach might be more effective than single-factor interventions in treating complex brain dysfunctions. Certainly, some of the most recent research supports the concept of broad-based supplementation for the treatment of mental function (Carroll et al. 2000; Schlebusch et al. 2000).

A psychostimulant was employed in conjunction with the micronutrient supplement in case 2 without apparent difficulty. In fact, the psychostimulant seemed to improve the cognitive symptoms that did not appear to be helped greatly by the nutrients. However, based on other cases involving both children and adults, clinical attempts to combine this supplement with other categories of conventional psychiatric medications should proceed with caution. There seem to be nutrient–medication interactions that have proven problematic in many cases (Popper 2001). In general, the nutrients have appeared to amplify the effects of the psychiatric medications, and the clinical experience of the physicians monitoring such patients suggests a need to decrease or discon-

tinue psychiatric medications after the micronutrient supplement has been introduced. In this respect, case 2 appears to be unusual in that the psychostimulant did not seem to require dose modification or discontinuation when used in combination with the micronutrient supplement. Moreover, as mentioned before, the true potential of this supplement for the treatment of ADHD has not yet been evaluated, although this case suggests that its impact on inattention may be limited.

Perhaps the most important unanswered question at this time relates to mechanism: How can ordinary dietary minerals and vitamins have such a large impact on mental function? Two issues are important to consider:

- In one sense, the large impact of this broad-based micronutrient supplement is exquisitely logical. As reviewed above, supplementation with many individual nutrients has been shown to improve mood (B vitamins, selenium, zinc, etc.), so it seems reasonable to speculate that a broader intervention might indeed have a larger effect.
- As discussed elsewhere (Kaplan et al. 2001), perhaps mood lability and explosive rage (as examples of mental dysfunction) are manifestations of inborn errors of metabolism in key neurobiological pathways, such as those responsible for neurotransmitter synthesis and uptake, membrane stabilization, second messenger signaling, and so on. If some of these metabolic pathways are particularly dependent on dietary nutrients that are deficient in these individuals, then supplementation might be sufficiently compensatory to enable these pathways to function more normally. Further exploration of this possibility may shed light on the role of many nutrients in brain function, in addition to lithium which is already the focus of so much research.

Future research

The two cases presented here constitute some of the pilot work carried out to determine whether further research of this micronutrient supplement is warranted (Kaplan et al. 2001). These two cases were selected from other pilot work because they were the only ones studied with ABAB designs. The findings suggest that this nutritional approach may have the capacity to stabilize mood significantly and that more systematic data collection is justified.

Much research still needs to be done before the impact of these preliminary findings can be properly evaluated. One randomized, placebo-controlled trial in adults with bipolar disorder is ongoing; another has been funded and will begin shortly. Several other randomized, controlled trials involving children are in the planning stages. Further research into safety and efficacy is also needed, and caution is particularly critical regarding nutrient interactions with psychiatric medications (Popper 2001).

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