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COMPLEMENTARY AND ALTERNATIVE THERAPIES FOR DOWN SYNDROME

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In their role as committed advocates, parents of children with Down syndrome have always sought alternative therapies, mainly to enhance cognitive function but also to improve their appearance. Nutritional supplements have been the most frequent type of complementary and alternative therapy used. Cell therapy, plastic surgery, hormonal therapy, and a host of other therapies such as massage therapy have been used. There is a lack of well-designed scientific studies on the use of alternative therapies in individuals with Down syndrome. Antioxidants hold theoretical promise for treatment of the cognitive, immune, malignancy, and premature aging problems associated with Down syndrome. Medications for treatment of Alzheimer's disease may also result in benefit for the population of individuals with Down syndrome.
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Over the last few decades, advocates of a wide range of alternative therapies have promised dramatic improvements in development and growth for children with Down syndrome (DS). Increasing numbers of families have sought complementary and alternative medical care (CAM) for themselves and their children with developmental disorders. Clinical research projects and centers are addressing the safety and efficacy of these alternative therapies [Kemper et al., 1999].

In an analysis of interviews conducted with 30 parents of children with DS, Prussing et al. [2005] found that CAM use reflected an effort to fulfill priorities not met in contemporary biomedical care, which views DS as a condition with a fixed, universal, and essentially pathological course. The parents articulated the goal of accepting their child as a person with DS while using CAM to maximize their health and developmental potential. Parents viewed seeking CAM as part of their role as a committed advocate and service coordinator for their child [Prussing et al., 2005]. Prussing et al. [2005] reported that nutritional supplements were the most commonly used CAM (Table 1). Of 30 families of children with DS, 21 (70.0%) had tried more than two therapies; 5 (16.7%) had tried one therapy, and 4 (13.3%) had tried none [Prussing et al., 2004]. Of the families who had used CAM therapies ($n = 26$), most parents (67%) had communicated none or only some of this use to their pediatricians [Prussing et al., 2004].

Almost all published trials have methodological shortcomings. There are few randomized, controlled trials. Most lack controls, have small sample sizes, have too short a duration, and target older individuals [Ani et al., 2000]. To detect a six-point (0.5 standard deviation) IQ difference, 170 individuals with DS with 85 in each arm of a clinical trial are needed [Kirkwood, 1988]. No single trial has come close to including 170 individuals.

Salman [2002] undertook a systematic, exhaustive review to identify relevant trials of dietary supplements and drugs and their effect on the cognitive function of subjects with DS. Using combined search strategies, he identified 28,068 studies, selected 428 as possibly relevant, and reviewed 109 that potentially fulfilled standard inclusion criteria. Eleven articles met the following criteria: all subjects had DS, the intervention included the use of drugs and/or dietary supplements, cognitive function was used as an outcome measure, the trials were controlled with a placebo group running concurrently or in a cross-over design, and there was randomization or pseudorandomization of the subjects. These 11 studies included a total of 373 randomized participants. Follow-up ranged between 1.3 and 36 months. None of 11 studies that met the methodological criteria used for scientific studies demonstrated a treatment effect.

This article will review the studies on the wide variety of CAM therapies for individuals with DS. In the review, we will discuss, when possible, the rationale, and the outcomes of studies *in vitro* and *in vivo* and in animals and humans. For some CAM therapies evidence to support or refute claims has not been published in the peer-reviewed literature. But for others, such as vitamin therapies, especially the use of antioxidants, and some medications, such as piracitam and donepezil, this information is available.

NUTRITIONAL SUPPLEMENTS

Combination Nutritional Therapies

Nutritional therapies for individuals with DS have a long and sometimes colorful history. In the 1960s in Germany and the United States, Dr. Henry Turkel claimed the "U" series of drugs, which included a mixture of 48 ingredients including thyroid globulin, organic ioidine, minerals, and bone meal would improve the intelligence and appearance of children with

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Table 1. Complementary and Alternative Therapies

- Nutritional supplements
  - Combination nutritional therapies: "U" series, Haps Caps, MSB Plus, NuTriVene-D
  - Antioxidants: vitamins A, B6, thiamine, niacin, C, E
  - Minerals: selenium, zinc
- Drugs
  - Donepezil
  - Piracetam
  - Vasopressin
  - Pituitary extract
  - Growth hormone
- Cell therapy
- Plastic surgery
- Other
  - Massage therapy, dietary modifications, animal therapy (therapeutic horseback riding), faith/prayer hearing, chiropractic care, homeopathy, osteopathy, neurologically based movement programs, aromatherapy, naturopathy, yoga

DS. Dr. Turkel calculated dosages by age so children were given one to four capsules three times per day. One study comparing "U" series with placebo included 24 children with DS 3 months to 11 years of age. No differences were found in the parameters measured, including IQ on the Stanford–Binet, growth, hemogram, urinalysis, or X-rays between the groups receiving placebo and "U" therapy [Bumbalo et al., 1964]. In 1981, in an uncontrolled and unblinded study, Harrell et al. [1981] reported that supplementary vitamins, minerals, and thyroid hormone improved IQ scores and caused "physical changes towards normal" among children with various types of mental deficiency with the best results in three children with DS. Subsequently, six randomized, controlled trials attempted to replicate these findings [Bennett et al., 1983; Coburn et al., 1983; Ellis and Tomporowski, 1983; Weathers, 1983; Smith et al., 1984; Bidder et al., 1989]. Four of the six trials met the research methodology criteria described by Salaman [2002] above. These studies included a total of 161 individuals with DS 6 months to 40 years of age. None showed any improvement in IQ, physical appearance, or general health. Haps Caps, another mixture of vitamins, minerals, and enzymes frequently given with thyroid hormone was promoted by traveling clinics run by Dr. Jack Warner of California. No studies of Haps Caps have been published.

In 1995, ABC-TVs "Day One" promoted a formula created by Dixie Lawrence Tafoya, the owner and operator of an adoption agency that specialized in finding homes for children with disabilities. She initially based her formula on Turkel's original "U" series but modified it for her own daughter. The television program described how Lawrence had adopted a girl with DS and had "tapped into medical data bases, scoured libraries, called research departments, talked to anyone who knew anything about the biochemistry of DS." The end result was a formula based on Turkel's original mixture but containing many more ingredients. Subsequently, the drug piracetam was added to the child's regimen [Leshin, 1997].

By the time "Day One" aired, this formula was scheduled to be produced by Nutri-Chem Labs as MSB Plus. In 1996, she withdrew her support from Nutri-Chem and began promoting a formula called NuTriVene-D, which is marketed by International Nutrition, Inc of Baltimore [Leshin, 1997]. This remains a popular intervention, although it has never been studied using clinical trials methodology.

Antioxidants

Using antioxidants to treat the cognitive, immune, malignancy, and premature aging problems associated with DS probably holds the most theoretical promise. Evidence suggests that increased oxidative stress defined as an imbalance between production of oxygen-derived free radicals and their removal by antioxidants may be involved in the pathology of DS. A gene on chromosome 21 codes for superoxide dismutase (SOD), a key enzyme in the metabolism of oxygen-derived free radicals to hydrogen peroxide. The increased activity of SOD in various tissues in DS [Sinet et al., 1975; Crosti et al., 1976; Feaster et al., 1977; Bjorksten et al., 1984; Brooksbank and Balazs, 1984; Kedziora et al., 1986; Kedziora et al., 1990; Tanabe et al., 1994; De-la-Torre et al., 1996] is thought to be due to a gene dosage effect. The increased hydrogen peroxide produced by the increase in SOD may then react with transition metals like iron to form the hydroxyl radical that can initiate lipid peroxidation resulting in damage to cell membranes [Ani et al., 2000]. The hydrogen peroxide is metabolized to water by glutathione peroxidase (GSH-Px, an endogenous antioxidant) or catalase [Halliwell and Gutteridge, 1989].

Several types of studies demonstrate the increase in SOD and the increased rates of lipid peroxidation. In animal studies, an increase in SOD is associated with increased rates of lipid peroxidation in the brain [Elroy-Stein et al., 1986; Ceballos-Picot et al., 1991, 1992; Peled-Kamar et al., 1995; Mirochnitchenko and Inouye, 1996]. In a study of the cerebral cortex of fetuses with DS compared with infants without DS, a 36% increase in lipid peroxidation was found in the fetuses with DS [Brooksbank and Balazs, 1984]. In cultured neurons from fetuses with DS, Busciglio and Yanker [1995] found about four times more free radicals and an increased level of lipid peroxidation compared with neurons from individuals without DS.

Theoretically, two mechanisms by which an increase in SOD activity can reduce immunity in DS would be by decreasing the concentration of superoxide radicals, which would decrease the microbicidal activity of leukocytes [Anneren and Bjorksten, 1984; Mirochnitchenko and Inouye, 1996] and by increasing hydrogen peroxide, which may damage immune cells and impair normal signal transduction processes involved in phagocyte activation [Mirochnitchenko and Inouye, 1996]. Neutrophils from individuals with DS have been shown to produce less superoxide radicals than those without DS [Anneren and Bjorksten, 1984; Kedziora et al., 1990]. In transgenic mice, a twofold overproduction of SOD by intraperitoneal macrophages resulted in an inhibition of extracellular release of superoxide radicals, increased intracellular production of hydrogen peroxide, and a reduction in microbicidal and fungicidal activity [Mirochnitchenko and Inouye, 1996]. Peled-Kamar et al. [1995] demonstrated increased activity of SOD in the thymus of transgenic mice. They also reported that this was associated with increased production of hydrogen peroxide and lipid peroxidation and that the thymus is more susceptible to lipopolysaccharide-induced apoptotic cell death. When they cultured bone marrow cells from transgenic mice under stressed conditions (e.g., addition of tumor necrosis factor), the bone marrow cells produced two to three times fewer granulocyte and macrophage colonies than control mice [Peled-Kamar et al., 1995].

Evidence now links increased oxidative stress with increased DNA damage in DS [Jovanovic et al., 1998; Pincheira et al., 1999]. In 166 matched pairs of individuals with DS and their siblings, Jovanovic et al. [1998] found significantly increased concentrations of 8-hydroxy-2-deoxyguanosine (a biomarker of oxidative damage to DNA) in the urine of individuals with DS. Pincheira et al.

[1999] found an increase in chromosomal damage in lymphocytes of individuals with DS compared with individuals without DS. By the addition of vitamin E (a powerful antioxidant) to the cell culture, the chromosomal damage could be reduced by more than 50%.

There is some evidence associating mental development in DS and oxidative stress. Sinet et al. [1979] found a positive correlation between the activity of GSH-Px, an edogenous antioxidant and IQ in 22 individuals with DS. Sinet et al. [1979] speculated that GSH-Px may play a role in preserving the cerebral status of individuals with DS. In a randomized controlled trial of vitamin E in Alzheimer's disease in individuals without DS, Sano et al. [1997] found significant beneficial effects.

De Haan et al. [1997] have studied premature aging and oxidative stress. In the normal mouse brain during aging, they found a significant increase in SOD: GSH-Px ratio and susceptibility to lipid peroxidation. In cultured murine cells transfected to have an increased SOD: GSH-Px ratio, they found characteristic features of senescence. In normal mouse cells exposed to hydrogen peroxide in culture, they also found features of senescense. In cells derived from children with DS, they found features of senescense that were not seen in cells from age-matched control children.

This body of evidence supports the theory of increased oxidative stress in DS and the role it might play in multiple areas of disease development. The possible prevention of cell damage with exogenous antioxidants has been one factor leading to multiple studies of vitamin treatment.

Antiamyloid strategies

Overexpression of the amyloid (APP) gene is thought to be one mechanism that results in increased beta-amyloid production and senile plaque formation in AD [Hardy, 1997]. Strategies to effect gene expression include modifying either the synthesis or degradation of the APP [Malther, 2001]. Therapies targeting the postproduction modification or clearance of beta-amyloid are the focus of intensive research [Schehr, 1994; Pennisi, 1999]. Vaccination is being considered as a way to prevent the deposition of beta-amyloid [Schenk et al., 1999].

Vitamins

Vitamin A

Three early studies reported poor absorption of and reduced serum vitamin A concentration in Down syndrome [Palmer, 1978; Matin et al., 1981; Shah et al., 1989], but other studies [Barden, 1977; Pueschel et al., 1990; Storm, 1990; Tanabe et al., 1994] did not report these findings. In one study by Palmer [1978], 23 children with Down syndrome 3–15 years of age were paired with their own siblings and randomly each pair was assigned to receive 1000 IU/kg/day of vitamin A or placebo for 6 months. Baseline DS groups experienced significantly more frequent infections than their siblings [$P < 0.01$]. In a follow-up of the DS/sibling pairs treated with vitamin A, the difference decreased and was insignificant. In control pairs not treated with vitamin A, by the fifth month of the study the differences remained significant [$P < 0.01$]. The methodology used to measure the frequency of infections, summing infection numbers, and the blinding was questionable.

Vitamin B6

Studies of vitamin B6/5-hydroxytryptamine (5-HTP) treatment were conducted to theoretically increase the serotonin levels [Coleman et al., 1985], which are reported to be reduced [Tu and Zellweger, 1965; Bazelon et al., 1967; Godridge et al., 1987]. Two uncontrolled studies reported improved muscle tone [Bazelon et al., 1967; Petre-Quadens and De Lee, 1975]. Two randomized trials failed to find any significant clinical improvements in 108 babies treated for 3 years [Pueschel et al., 1980; Coleman et al., 1985].

Other Vitamins

In individuals with DS, trials of thiamine and niacin have also demonstrated no effect. Lonsdale and Kissling [1986] treated 11 children 8–16 years of age with thiamine and measured their scores on the Stanford–Binet IQ scale. Heaton-Ward et al. [1962] treated 12 hospital inpatients with DS 6–36 years of age with niacin and measured their function on the Stanford–Binet.

Minerals

Selenium

Selenium is a component of GSH-PX, which is part of the body's endogenous antioxidant system [Sinet, 1982]. In one uncontrolled study, 48 children with DS 1–16 years of age were treated with 10 μg selenium/kg/day for 6 months. Concentrations of immunoglobulin G2 and G4 increased by up to 33 and 75%, respectively, and participants reported fewer infections during the study period [Anneren et al., 1990]. However, almost half of the participants were lost to follow-up, making it difficult to interpret the data. In another study, 7 individuals with DS aged 1–54 years were given 25 μg selenium/kg/day for 0.3 to 1.5 years. They reported a 25% increase in the activity of GSH-Px and a 24% reduction in the SOD:GSH-Px ratio in the supplemented group compared with the 10 unsupplemented individuals with DS [Antila et al., 1990].

Zinc

Zinc is part of the cytosolic copper–zinc–SOD enzyme [Sinet, 1982]. Of 16 studies comparing serum levels of zinc in individuals with and without DS, 13 showed significantly reduced levels in individuals with DS and 3 found no difference [Ani et al., 2000].

Ani et al. [2000] reviewed seven uncontrolled open zinc trials with pre- and posttreatment measurements in a total of 168 individuals with DS aged 2 to 22 years. Although they all reported mainly laboratory evidence for beneficial effects on the immune function, Ani and coworkers stated that the data were difficult to interpret. One randomized controlled trial of zinc in DS [Lockitch et al., 1989] lasted 6 months with crossover for another 6 months in 64 individuals with DS 1–19 years of age. They found no significant changes in lymphocyte function, complement levels, or number of infections. However, the zinc-treated group had significantly fewer episodes of cough [$P = 0.03$] and, in children less than 10 years of age, significantly fewer cough days [$P = 0.01$].

Two *in vitro* studies indicated a potential benefit of zinc supplementation. Fabris et al. [1984] added zinc to the serum of individuals with DS and found an increase in their thymic factor to levels seen in typical individuals and a reduced concentration of the serum thymic inhibitory factor. Chiricolo et al. [1993] found that individuals with DS who were supplemented for 4 months with 1 mg zinc /kg/day had an increase in the *in vitro* incorporation of thymidine into their phytohaemagglutin-stimulated lymphocytes similar to individuals without DS.

DRUGS

Donepezil

The characteristic neuropathology of Alzheimer's disease (AD) is the formation of amyloid plaques and neurofibrillary tangles, loss of cortical brain matter, synaptic and neuronal loss, and the pres-

ence of inflammatory changes [Esiri, 2001]. Deficits in cerebral neurotransmitters, such as acetylcholine, neuradrenaline, and serotonin characterize AD neurochemically [Poirier et al., 1999; Giacobini, 2003]. The "cholinergic hypothesis of AD" is based on the findings that suggest that the principal chemical deficiency is degeneration of cholinergic neurons, neocortical deficits in choline acetyltransferase, reduced choline uptake, and reduced actylcholine release [Farlow, 2002]. Based on this hypothesis, the goal of drug development in AD has been to enhance selective cholinergic transmission in the brain. The aim of drugs has been to increase the supply of choline by stimulating cholinergic receptors or by reducing acetlycholine metabolism by inhibiting cholinesterase action. To this goal, donepezil and galantamine are selective inhibitors of acetylcholinesterase (AchE); rivastigmine is a dual inhibitor of AchE and butyrlcholinestrease [AchE]; and memantine is a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) [Prasher, 2004].

In the general population, as a result of numerous studies, it has been established that patients with AD do benefit clinically with antidementia therapy. In one study of 431 patients with AD randomized to donepezil and placebo for 54 weeks, the treated group maintained a higher level of function 72% longer [Mohs et al., 2001]. In contrast, only a few studies have been published in individuals with DS and all have studied donepezil [Kishnani et al., 1999; Lott et al., 2002; Prasher et al., 2002; Heller et al., 2003; Johnson et al., 2003].

In the first study of donepezil hydrochloride treatment in 4 DS adults 27–64 years of age treated for 6 months, Kishnani et al. [1999] found improvement in the Vineland Adaptive Behavior Scale in the two younger adults without dementia. Side effects of short-term agitation and diarrhea resolved. Lott et al. [2002] reported results from an open-label study of donepezil to treat dementia in 9 adult patients with DS for 83–182 days. A significant improvement in dementia scores was reported in the treated group. Heller et al. [2003] reported improvement in expressive language performance in a group of 24 adults with DS who participated in a 24-week, open-label, clinical trial of donepezil. In a 12-week trial of donepezil in 19 adults with DS divided into treatment and control groups, Johnson et al. [2003] found improvement in language scores but not in cognitive subtests, behavior scores, or caregiver ratings. Prasher et al. [2002] conducted a 24-week, double-blind, placebo controlled, parallel-group trial on 27 adults with DS and AD. The donepezil group had nonstatistically significant reduction in deterioration in the Dementia Scale for Mentally Retarded Persons, the Severe Impairment Battery, and the Adaptive Behavior Scale, but the Neuropsychiatric Inventory scores showed less improvement when compared to the placebo group. They reported that, although side effects including diarrhea, insomnia, fatigue, and nausea did occur, the drug was generally well tolerated. This area of research shows promise in improving the language function and slowing the dementia associated with Alzheimer's disease in individuals with Down syndrome.

The use of drugs to prevent dementia is becoming routine in the general population and is likely to become first-line treatment for AD in adults with DS [Prasher, 2004]. Other drug therapies that are being developed to treat AD may be helpful in individuals with DS. These might include metal chelation agents (e.g., clioquinol), nonsteroidal antiinflammatory drugs (e.g., indomethacin); antioxidants (e.g., vitamin E); hormones (e.g., estradiol); herbs (e.g., Gingko biloba); and vitamins such as folic acid [Marx, 1996; Capone, 2004; Prasher, 2004].

Piracetam

In 1995, media reports on "Day One" and "Nightline" publicized the hypothesis that the combination of nutritional supplements and piracetam improved the cognitive function of children with DS. This was based on the testimony of at least one mother who claimed that, on this combination, her 6-year-old daughter's "concentration and awareness improved. Her speech has improved to the point that she is finally saying phrases and sentences. Improvement is slow but she is finally making some." [Lobaugh et al., 2001]. Based on this testimonial, it is believed that thousands of children have received the drug [Lobaugh et al., 2001].

Piracetam, a cyclic derivative of gamma-aminobutyric acid (GABA) is a nootropic drug, a psychoactive drug that is postulated to enhance cognitive function and brain dysfunction in Alzheimer disease, developmental dyslexia, and stroke [Vernon and Sorkin, 1991]. In a number of animal models, piracetam has been shown to improve cognitive performance. In a study of the effects of a range of doses of piracetam in the Ts65Dn mouse model of Down syndrome, control mice improved performance in platform tasks on the lower of the three doses of piracetam but the Ts65Dn mice did not improve performance on piracetam [Moran et al., 2002].

Pelsman et al. [2003] studied an *in vitro* model of neuronal degeneration mediated by oxidative stress using normal human cortical neurons treated with H_2O_2, and cortical neurons from individuals with DS. They studied GVS-III (an analog of piracetam) and found that it inhibited the accumulation of intracellular free radicals and lipid peroxidation damage in neurons treated with H_2O_2 or $FeSO_4$, suggesting an antioxidant mechanism of action. In DS cortical cultures, chronic treatment with GVS-111 significantly reduced the appearance of degenerative changes and enhanced neuronal survival.

Lobaugh et al. [2001] at Hospital for Sick Children in Toronto published a double-blind crossover study on the use of piracetam in 25 individuals 6–13 years old with DS. They recruited moderate to high-functioning children with DS. Exclusion criteria included hearing, vision, language, or other physical or cognitive limitations that would interfere with their ability to complete the test battery. Children with known problems in swallowing pills, use of piracetam during the previous 6 months, and concurrent use of megavitamins were excluded. The children were evaluated on 14 tests that covered attention, cognitive function, learning and memory, perceptual abilities, executive function, and fine motor and visuomotor skills. Parents and teachers completed standardized questionnaires. Eighteen of 25 children completed the study; 3 withdrew due to difficulty swallowing capsules and 1 because of surgery. Piracetam therapy did not significantly improve cognitive performance over placebo use. Seven children had side effects associated with central nervous system (CNS) stimulatory effects: aggressiveness ($n = 4$), agitation or irritability ($n = 2$), sexual arousal ($n = 2$), poor sleep ($n = 1$), and decreased appetite ($n = 1$).

Some comments on the study of piracetam have expressed concerns that the analysis, interpretation, and discussion misinterpreted the data and the positive effect of piracetam might have been overlooked [Black, 2001; Croom, 2001].

Other Drugs

Several other trials of medication that met the criteria described above by Salman [2002] did not demonstrate a positive effect. Eisenberg et al. [1984] treated nine subjects 10 to 42 years of age with DS with vasopressin and measured their function with word list and visual

verbal paired associated tasks. Berg et al. [1961] treated three children with DS 16 months to 4 years of age with pituitary extract and measured their function on the Griffiths mental developmental scale. Treatment of children with DS with growth hormone has resulted in an increase in the velocity of growth [Torrado et al., 1991; Anneren et al., 1999] but there have been no publications on the effect on the final height. The Lawson Wilkins Pediatric Endocrine Society has expressed concern about the efficacy and possible additional increased risks for developing leukemia in the population of children with DS treated with growth hormone [Lawson Wilkins Pediatric Endocrine Society Board of Directors and Drug and Therapeutics Committee, 1993].

CELL THERAPY

Cell therapy is the administration of freeze-dried or lyophilized cells derived from fetal tissues of sheep and rabbits and has been used mainly in Europe to treat millions of people with a variety of illnesses and conditions. One form of cell therapy, sicca cell therapy, consists of the subcutaneous injection of freeze-dried or lyophilized fetal brain cells. Although sicca cell treatments are not legally available in the United States, families have traveled to Germany for treatment and received lyophilized material by mail. As a foreign protein, sicca cell injections may induce allergic or hypersensitivity reactions. Theoretical concerns include the possibility that viruses may be transmitted with these injections [Van Dyke et al., 1990].

Sicca cell treatment is purported to result in improvement of cognitive, motor, language, social function, enhancement of growth, and removal or amelioration of some of the dysmorphic features of DS. In two studies of individuals with DS, one a double-blind prospective study in Canada in 59 individuals [Black et al., 1966] and the other a study in England of 10 experimental and 10 control subjects [Bardon, 1964], no positive effect on cognitive function was reported.

Although sicca cell therapy is illegal in the United States, van Dyke et al. [1990] reported that 11% ($n = 21$) of a patient population of 190 individuals with Down syndrome had received sicca cell therapy. In a retrospective analysis, the 21 children (mean age 48 months) who had received sicca cell therapy in multiple injections usually before 5 years of age every 6 to 12 months were compared to 21 children with DS matched demographically and for cardiac history. The groups were compared on 18 variables measuring growth, social adaptive skills, motor skills, and cognitive development. There were no significant differences in any of these comparisons [van Dyke et al., 1990].

PLASTIC SURGERY

The face of the child or adult with DS is recognizable to most people and stereotypic assumptions related to cognitive capacity are made. One reason proposed for facial plastic surgery is to change the facial features of the person with DS so that they are not recognized as having DS. Theoretically this would improve their physical appearance and social acceptance. The main other reason is to decrease the size of the tongue to make speech clearer, improve breathing, diminish drooling, facilitate chewing and swallowing [Rozner, 1983; May and Turnbull, 1992], and improve appearance. In a study by Pueschel et al. [1986], most parents (72%) felt that the children's facial features did not negatively affect their social development and 85% saw their children as well accepted by society; whereas 63% of physicians felt that the children's facial features negatively affect their social development and only 4% see the children as well accepted by society. Both parents (92%) and physicians (76%) were concerned about the risk of the operation. Only 13% of the parents favored facial plastic surgery for children with DS.

The number of procedures included in facial plastic surgery depends on the surgeon's preference and the child's needs. Most often they include wedge resection of the tongue [Katz and Kravetz, 1989] and altering of the appearance of the eye with removal of epicanthal folds and straightening out the oblique eyelid axis. Less frequently, they include reduction of the lower lip and implants of silicone or cartilage at the chin, nasal bridge, and cheeks. Complications have included suture dehiscence, an additional lengthening procedure if the tip of the tongue is too short [Lemperle and Radu, 1980], and infection and dislocation of silicone implants [Olbrisch, 1982].

Reports from the early 1980s relied mainly on questionnaires and anecdotal reports of subjective impressions of clarity and production of speech and facial appearance. In these reports, parents and surgeons indicated satisfaction with the results in 77–95% of cases [Olbrisch, 1982; Lemperle, 1985]. More recent studies have included objective measures and opinions of uninvolved observers and have not reported improvement in speech. In a study of 18 children who underwent tongue-reduction surgery, Parsons et al., [1987] reported no significant difference in articulation errors at early or at 6-month follow up. In another group of 23 children with partial glossectomy, pre- and postoperative audiotaped samples of spoken words and connected speech were rated by three lay people and by three professionals who found no differences in acoustic speech intelligibility [Margar-Bacal et al., 1987].

In a recent survey of 250 parents of children with DS, the majority did not support the surgery [Goeke et al., 2003]. A study comparing the perceptions of their children's personal, physical, and social function by parents of children with and without plastic surgery produced little evidence for a positive impact [Kravetz, 1992]. A 1992 survey of 132 Italian schoolteachers showed a greater acceptance of children with Down syndrome as they are by people with daily experience with them. Teachers who were less involved with the children were more accepting of plastic surgery for children with DS [Saviolo-Negrin and Cristante, 1992]. In one study, lay raters found the postoperative appearance of children's faces to be slightly less attractive than the preoperative appearance [Arndt et al., 1986]. But, in a study examining how 277 adolescents perceived slides of the faces of 8 patients with Down syndrome before and after plastic surgery, overall there was improvement in the dimensions of attractiveness, intelligence, good-heartedness, and social appeal [Strauss et al., 1988].

Facial plastic surgery for children with DS remains controversial. Published studies frequently offer almost no rationale for the surgery probably assuming that results are self-evident and that parent satisfaction alone is sufficient justification [Katz and Kravetz, 1989].

CONCLUSIONS

Multiple types of CAM therapies are used to prevent and treat the cognitive problems associated with DS. Most CAM therapies specific for DS have few or no published studies, and the studies that follow the expectations of scientific methodology demonstrate no effect [Salman, 2002]. Other therapies often used for children with DS have not been evaluated in the peer-reviewed literature specifically in this population (e.g., massage therapy, herbal therapies, dietary modifications, animal therapy or therapeutic horseback riding, faith/prayer healing, chiropractic, homeopathy, osteopathy,

neurologically based movement programs, aromatherapy, naturopathy, and yoga).

The search for treatments for Alzheimer's disease and the search for the prevention of the progression of the pathological changes noted in the brains of children with DS beginning in late pregnancy [Wisniewski et al., 1996] are intersecting. Novel therapies are being imagined and developed that will focus on treatments that are neuropharmacologic (e.g., donepezil), neurogenetic (e.g., antiamyloid strategies), and neuroprotenomic (e.g., antioxidants; antiinflammatory agents) [Capone; 2004]. ■

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