

## Down Syndrome

## ABSTRACTS

- Barden, 1977. Vitamin A and carotene values of institutionalized mentally retarded subjects with and without Down's syndrome.
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- Buxhoeveden D, 2002 Quantitative comparison of radial cell columns in children with Down's syndrome and controls.
- Carratelli M, 2001. Reactive oxygen metabolites and prooxidant status in children with Down's syndrome.
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- Conners FA, 2001. Memory training for children with Down syndrome.
- Fragar., 1985. A double blind study of vitamin B-sub-6 in Down's syndrome infants: II. Cortical auditory evoked potentials.
- Hildmann A, 2002. [Hearing Disorders in Children with Down's Syndrome] [Article in German]
- Isacson O, 2002 Alzheimer's disease and Down's syndrome: roles of APP, trophic factors and ACh.
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- Kitzmueller E, 2001. Carbohydrate handling enzymes in fetal Down syndrome brain.
- Nijjar RK, 2002. Olfactory impairment increases as a function of age in persons with Down syndrome.
- Otsuka Y, 2002. Enhancement of lipopolysaccharide-stimulated cyclooxygenase-2 mRNA expression and prostaglandin E(2) production in gingival fibroblasts from individuals with Down syndrome.
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- Vitamin A and carotene values of institutionalized mentally retarded subjects with and without Down's syndrome.**

Barden, H. S. U Illinois

Journal of Mental Deficiency Research 1977 Mar Vol 21(1) 63-74

Assessed vitamin A and carotene values of 44 3-34 yr old Down's syndrome, 56 3-35 yr old non-Down's Syndrome mentally retarded, and 40 normal 1-25 yr old Ss. Dietary and environmental uniformity was maintained by utilizing Down's and non-Down's Ss residing in the same institution. Results show that Down's Ss showed vitamin A values that were significantly higher than those of the non-Down's retarded Ss and similar to those of the normal Ss. Carotene values were similar in the Down's and non-Down's retarded groups, but were significantly higher than those of the normal Ss. This difference in carotene is seen as reflecting in part the high level of carotenoid products in the institutional diet. Carotene/vitamin A ratio values are reported, and the possibility that relatively high ratio values reflected a decreased efficiency in converting carotene to vitamin A is discussed. It is suggested that Down's Ss may suffer some impairment in the utilization of vitamin A at its site of action.

## **Down Syndrome Cell Adhesion Molecule is conserved in mouse and highly expressed in the adult mouse brain.**

Barlow GM, Micales B, Lyons GE, Korenberg JR. Department of Medical Genetics, Cedars-Sinai Medical Center and UCLA, Los Angeles CA (USA).

Cytogenet Cell Genet 2001;94(3-4):155-162

Down Syndrome (DS) is a major cause of mental retardation and is associated with characteristic well-defined although subtle brain abnormalities, many of which arise after birth, with particular defects in the cortex, hippocampus and cerebellum. The neural cell adhesion molecule DSCAM (Down syndrome cell adhesion molecule) maps to 21q22.2[→]q22.3, a region associated with DS mental retardation, and is expressed largely in the neurons of the central and peripheral nervous systems during development. In order to evaluate the contribution of DSCAM to postnatal morphogenetic and cognitive processes, we have analyzed the expression of the mouse DSCAM homolog, Dscam, in the adult mouse brain from 1 through 21 months of age. We have found that Dscam is widely expressed in the brain throughout adult life, with strongest levels in the cortex, the mitral and granular layers of the olfactory bulb, the granule cells of the dentate gyrus and the pyramidal cells of the CA1, CA2 and CA3 regions, the ventroposterior lateral nuclei of the thalamus, and in the Purkinje cells of the cerebellum. Dscam is also expressed ventrally in the adult spinal cord. Given the homology of DSCAM to cell adhesion molecules involved in development and synaptic plasticity, and its demonstrated role in axon guidance, we propose that DSCAM overexpression contributes not only to the structural defects seen in these regions of the DS brain, but also to the defects of learning and memory seen in adults with DS. Copyright 2002 S. Karger AG, Basel

## **Effects of a single transdermal nicotine dose on cognitive performance in adults with Down syndrome.**

Bernert G, Sustrova M, Sovcikova E, Seidl R, Lubec G. Department of Pediatrics, University of Vienna, Austria.

J Neural Transm Suppl 2001;(61):237-45

Subjects with Down syndrome exhibit various types of cognitive impairment. Neuropathological and neurochemical studies revealed similarities between Down syndrome and Alzheimer's disease, cholinergic deficits being the most consistent findings. To explore the potential for cognitive enhancement utilizing nicotinic stimulation, 8 patients with Down syndrome (aged 18.5-31 years) received placebo and a single dose of transdermal nicotine (5 mg patch) over 2h in a single-blind, within-subjects repeated measures design. Auditory event-related potentials (ERPs) and neuropsychological tests, comprising digit symbol performance subtest from WAIS-R and the Frankfurt Attention Inventory (FAIR) were performed. Effects of nicotine administration in Down syndrome individuals were a decrease of ERP-P3 latency in 7 of 8 subjects (electrode position Cz: 386.9±24.0 ms vs. 363.1±26.9.2 ms, placebo vs. nicotine, respectively; P = 0.058) and an increase of ERP-P3 amplitude in 6 of 8 subjects (electrode position Cz: 17.4±5.5 vs. 18.0±4.5 microV, placebo vs. nicotine respectively; P = 0.725). Neuropsychological tests exhibited improvements in digit symbol performance subtest in 4 of 8 subjects and 7 of 8 subjects in the Frankfurt Attention Inventory. These results suggest that stimulating central nicotinic receptors might have an acute cognitive benefit in young adult Down syndrome subjects.

## **Quantitative comparison of radial cell columns in children with Down's syndrome and controls.**

Buxhoeveden D, Fobbs A, Roy E, Casanova M. The Medical College of Georgia and Downtown VAMC, Augusta, Georgia, USA.

J Intellect Disabil Res 2002 Jan;46(Pt 1):76-81

No one has examined the configuration of the minicolumns in Down's syndrome (DS) brains even though these are a basic functional unit of the cortex. In the present study, the authors used computerized imaging to examine minicolumns in the posterior superior temporal gyrus in both the brains of patients with DS and normal controls. They compared the brains of children aged 4 and 6 years with those of adults for both people with DS and the normal population. Columns in the brains of two DS children aged 4 and 6 years were almost the same size as those of the adults with DS. The neuropil space in the periphery of the columns was also considerably wider. In contrast, minicolumns in aged-matched control children were smaller, both relatively and absolutely, when compared to the mean size of adult columns. The size of the minicolumns in the normal children apparently corresponded to the overall brain size, whereas the large columns in children with DS appeared to be independent of brain size, at least in area Tpt. This seems to reflect a rapid ageing process that is striking when compared to normal controls. Columns in adults with DS were large and less cell dense, while brain volumes were significantly smaller than in controls. This combination suggests reduced neuronal complexity based on a decrease in processing units, which supports previous findings of decreased cell numbers and synaptic diminution in DS brains.

## **Reactive oxygen metabolites and prooxidant status in children with Down's syndrome.**

Carratelli M, Porcaro L, Ruscica M, De Simone E, Bertelli AA, Corsi MM. Diacron S.r.l., Diagnostic Division, Grosseto, Italy.

Children with Down's syndrome suffer many diseases among which cardiovascular diseases, increased susceptibility to infections, leukemia, endocrine alterations, immune defects, nutritional disturbance and mental retardation have clinical relevance. It has been suggested that the pathogenesis of Down's syndrome involves reactive oxygen species arising from a mutation in gene encoding, which disproportionately elevates superoxide dismutase activity. Reactive oxygen species and total antioxidant capacity were evaluated using two new spectrophotometric methods in a selected group of 40 children with Down's syndrome and in 20 apparently healthy children used as controls. Reactive oxygen species were significantly higher ( $< 0.05$ ) in children with Down's syndrome than in controls: 452 (+/- 72) U.Carr vs. 270 (+/- 66) U.Carr respectively. Total antioxidant capacity was significantly higher ( $< 0.05$ ) in controls than in children with Down's syndrome: 380 (+/- 52) micromol hypochlorous acid (HClO)/ml vs. 281 (+/- 33) micromol HClO/ml, respectively. In fact, thiol groups (sulfhydryl) were significantly higher ( $< 0.05$ ) in controls than in children with Down's syndrome: 644 (+/- 78) micromol/l vs. 462 (+/- 54) micromol/l, respectively. Our data show how to simply measure chemical indices of oxidative status in serum samples from children with Down's syndrome. We determined the plasmatic activities of reactive oxygen metabolites and oxidative defense molecules. Accumulated macromolecular damage may be one of the causes of some of the abnormalities that are considered part of the syndrome. Therefore, children with Down's syndrome have to cope with a significant prooxidant environment. Oxidative stress causes alterations such as atherosclerosis, early aging, immunological defect and neurologic disorders in Down's syndrome patients. The new test available for measuring reactive oxygen species in serum proved to be reliable and useful as an early marker of tissue damage.

### **A double blind study of vitamin B-sub-6 in Down's syndrome infants: I. Clinical and biochemical results.**

Coleman, Mary et al Georgetown U School of Medicine

Journal of Mental Deficiency Research 1985 Sep Vol 29(3) 233-240

19 infants with Down's Syndrome participated in a double-blind study of the clinical effects of pharmacological doses of vitamin B-sub-6 administration, starting under 8 wks of age and continuing until 3 yrs of age. 10 Ss received the vitamin and 9 the placebo. No statistically significant differences were found between the 2 groups in mental age, height, weight, cranial circumference, or tongue protrusion. Vitamin B-sub-6 significantly elevated whole blood 5-hydroxytryptamine during the 1st yr. A study of side effects conducted on a larger open population of 400 Down's Syndrome patients (from infants to aged 12 yrs) found vitamin B-sub-6 to be relatively safe when administered over long periods of time, with photosensitive blisters as the major complication.

### **Memory training for children with Down syndrome.**

Connors FA, Rosenquist CJ, Taylor LA. University of Alabama, USA. fconnors@bama.ua.edu

Downs Syndr Res Pract 2001 Oct;7(1):25-33

One well-established fact concerning cognitive and language development in individuals with Down syndrome is that working memory is particularly poor, with auditory working memory worse than visual working memory. Working memory serves the functions of control, regulation, and active maintenance of information and is critical in daily complex cognitive activities. Thus, there is a strong need to find effective and practical interventions targeted at improving working memory in individuals with Down syndrome. The present paper reviews research on rehearsal training and concludes that it can be used successfully to increase working memory in individuals with Down syndrome. However, there are still questions about whether auditory working memory can be improved reliably, whether improvement can be maintained over the long term, and whether improvement exists beyond any effect of increased attention. We describe our in-progress study which addresses these concerns.

### **A double blind study of vitamin B-sub-6 in Down's syndrome infants: II. Cortical auditory evoked potentials.**

Fragar, Joseph; Barnet, Ann; Weiss, Ira; Coleman, Mary Montefiore Hosp & Medical Ctr, Dept of Medicine, New York, NY

Journal of Mental Deficiency Research 1985 Sep Vol 29(3) 241-246

Recorded cortical auditory evoked potentials (CAEPs) at 1 and at 3 yrs of age in 19 children with Down's Syndrome participating in a double-blind trial of vitamin B-sub-6 and placebo that was begun in early infancy and continued for 3 yrs. CAEPs have previously been shown to have abnormally high amplitude in Down's Syndrome patients. The CAEPs of the Ss in the B-sub-6-treated and placebo groups were compared. Only minor effects were found in the CAEPs recorded at 1 yr of age. At 3 yrs of age, however, comparison of the B-sub-6-treated group and the placebo group revealed significant differences in both amplitudes and latencies of CAEP components. Peak-to-peak amplitudes of prominent components were significantly lower in B-sub-6-treated Ss than in their placebo controls. Amplitude correlated in some cases with whole blood serotonin levels. Latencies for several prominent evoked peaks were significantly longer in B-sub-6-treated Ss. Findings suggest a difference in neurodevelopmental trajectories that seems

to be a pharmacological effect of B-sub-6 administration. (17 ref)

### **[Hearing Disorders in Children with Down's Syndrome] [Article in German]**

Hildmann A, Hildmann H, KeBler A. Univ. Hals-Nasen-Ohren-Klinik der Ruhr-Universität Bochum (Direktor: Prof. Dr. med. H. Hildmann).

Laryngorhinootologie 2002 Jan;81(1):3-7

Abstract. Among 4947 children in an outpatients unit for hearing disorders 102 children with Down's syndrome were seen and checked for hearing disorders. 57 had hearing deficiencies, 50 (88 %) conductive hearing loss, 4 (7 %) combined and 3 (5 %) a sensory neural hearing loss. Compared to other publications the number of very young children was very high. 32 patients under two years of age had a hearing disorder. The results underline the necessity of early diagnosis and follow up also in children with normal reactions during the first presentation. Early diagnosis enables early treatment, conservative, surgical or fitting with hearing aids, especially important in the rehabilitation of these children. Hearing aids may be given temporarily imploring communication during the development of the child.

### **Alzheimer's disease and Down's syndrome: roles of APP, trophic factors and ACh.**

Isacson O, Seo H, Lin L, Albeck D, Granholm AC. Neuroregeneration Laboratory, McLean Hospital, Program in Neuroscience and Dept of Neurology, Harvard Medical School, Belmont, MA 02478-9106, USA. isacson@helix.mgh.harvard.edu

Trends Neurosci 2002 Feb;25(2):79-84

Recent therapeutic investigations of Alzheimer's disease (AD) have been guided by two seemingly opposed hypotheses: the amyloid cascade theory, which favors the amyloid plaques as the cause of AD; and the cholinergic theory, which favors cholinergic neuron loss as the cause. New investigations indicate that the synthesis and processing of the amyloid precursor protein (APP) is linked to the trophic actions of nerve growth factor. A pathological cascade in both AD- and Down's syndrome-related memory loss could be triggered by alterations in APP processing or ACh-mediated neuronal function, or both, which in turn trigger the overexpression of amyloid beta, synaptic malfunction and trophic factor loss in target regions. This eventually leads to synaptic and dendritic loss with age.

### **Vitamin E and Alzheimer's disease in subjects with Down's syndrome.**

Jackson, C. V.; Holland, A. J.; Williams, C. A.; Dickerson, J. W. U Surrey Div of Nutrition & Food Science, Guildford, England

Journal of Mental Deficiency Research 1988 Dec Vol 32(6) 479-484

Tested the hypothesis that a low level of serum Vitamin E would be associated with a likelihood of dementia in 24 Ss (aged 30+ yrs) with Down's syndrome. Blood samples were drawn, and evidence of deterioration in self-care skills was assessed. Nine Ss showed evidence of Alzheimer's disease (AD), and 9 did not. Plasma Vitamin E levels measured in Ss with AD were lower than in Ss without AD. It is suggested that there may be an interaction between risk of AD and the protective action of Vitamin E.

### **Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome.**

James SJ, Pogribna M, Pogribny IP, Melnyk S, Hine RJ, Gibson JB, Yi P, Tafoya DL, Swenson DH, Wilson VL, Gaylor DW. Food and Drug Administration-National Center for Toxicological Research, the Division of Biochemical Toxicology, Jefferson, AR 72079, USA. jjames@nctr.fda.gov

Am J Clin Nutr 1999 Oct;70(4):495-501

BACKGROUND: Down syndrome, or trisomy 21, is a complex genetic disease resulting from the presence of 3 copies of chromosome 21. The origin of the extra chromosome is maternal in 95% of cases and is due to the failure of normal chromosomal segregation during meiosis. Although advanced maternal age is a major risk factor for trisomy 21, most children with Down syndrome are born to mothers < 30 y of age. OBJECTIVE: On the basis of evidence that abnormal folate and methyl metabolism can lead to DNA hypomethylation and abnormal chromosomal segregation, we hypothesized that the C-to-T substitution at nucleotide 677 (677C < T) mutation of the methylenetetrahydrofolate reductase (MTHFR) gene may be a risk factor for maternal meiotic nondisjunction and Down syndrome in young mothers. DESIGN: The frequency of the MTHFR 677C < T mutation was evaluated in 57 mothers of children with Down syndrome and in 50 age-matched control mothers. Ratios of plasma homocysteine to methionine and lymphocyte methotrexate cytotoxicity were measured as indicators of functional folate status. RESULTS: A

significant increase in plasma homocysteine concentrations and lymphocyte methotrexate cytotoxicity was observed in the mothers of children with Down syndrome, consistent with abnormal folate and methyl metabolism. Mothers with the 677C < T mutation had a 2.6-fold higher risk of having a child with Down syndrome than did mothers without the T substitution (odds ratio: 2.6; 95% CI: 1.2, 5.8;  $P < 0.03$ ). CONCLUSION: The results of this initial study indicate that folate metabolism is abnormal in mothers of children with Down syndrome and that this may be explained, in part, by a mutation in the MTHFR gene.

### **Carbohydrate handling enzymes in fetal Down syndrome brain.**

Kitzmueller E, Greber S, Fountoulakis M, Lubec G. Department of Pediatrics, University of Vienna, Austria.

J Neural Transm Suppl 2001;(61):203-10

Impaired glucose metabolism in adult Down Syndrome (DS) has been well-documented in vivo and information on the underlying biochemical defect i.e. aberrant glucose handling enzymes is already available. Nothing is known on carbohydrate handling, however, in early life of DS patients, when no secondary phenomena as e.g. Alzheimer-like neuropathology occur in the brain yet. We therefore determined a series of key enzymes of carbohydrate metabolism in fetal control and DS brain during the early second trimester. We used two-dimensional electrophoresis with subsequent MALDI characterization and specific software for quantification of protein spots. We observed comparable levels of phosphoglycerate mutase, phosphoglycerate kinase 1; fructose-biphosphate aldolase A, fructose biphosphate aldolase C; ribose-phosphate pyrophosphokinase 1; D-phosphoglycerate dehydrogenase, 6-phosphogluconolactonase; aflatoxin B1 aldehyde reductase 1, aldose reductase; inosine-5'-monophosphate dehydrogenase 2; galactokinase, in brain of fetal controls and DS. We conclude that our biochemical findings point to the fact that DS patients start early life with unchanged glucose handling, pentose phosphate shunt, glycolysis, sugar aldehyde, guanine nucleotide- and ribonucleoside formation and galactose metabolism.

### **Olfactory impairment increases as a function of age in persons with Down syndrome.**

Nijjar RK, Murphy C. Department of Psychology, San Diego State University, San Diego, CA, USA

Neurobiol Aging 2002 Jan;23(1):65-73

Neuropathology similar to that found in the brains of patients with Alzheimer's disease (AD) has consistently been observed in older individuals with Down syndrome (DS) and this neuropathology is particularly prevalent in areas involved in olfaction. The present study investigated the effects of age on the expression of olfactory impairment in Down syndrome to address the hypothesis that older adults with DS show greater deficits in olfactory function compared with younger persons with DS and compared with age and IQ matched control groups. Between group differences showed that persons with DS had significant deficits in olfactory functioning compared to the two control groups. Further, within the DS group, older adults performed more poorly than the young adults or children. Results support the hypothesis that in a group of persons at risk for AD because of DS, olfactory impairment is greater in older individuals, suggesting progressive impairment over time. Deficits in olfactory function may be useful in signalling incipient dementia in DS.

### **Enhancement of lipopolysaccharide-stimulated cyclooxygenase-2 mRNA expression and prostaglandin E(2) production in gingival fibroblasts from individuals with Down syndrome.**

Otsuka Y, Ito M, Yamaguchi M, Saito S, Uesu K, Kasai K, Abiko Y, Mega J. Department of Dentistry for the Disabled, Nihon University School of Dentistry at Matsudo, 870-1, Sakaecho-Nishi 2, Matsudo, 271-8587, Chiba, Japan

Mech Ageing Dev 2002 Mar 31;123(6):663-74

It is well known that Down syndrome (DS) is a premature ageing syndrome. Periodontal disease in individuals with DS develops rapidly and extensively in a relatively younger age bracket compared with that in healthy controls. The mechanisms involved in the periodontal inflammatory processes in DS patients are not fully understood. In the present study, the non-inflamed gingival fibroblasts isolated from seven patients with DS (DGF) and seven healthy controls (NDGF) were stimulated with lipopolysaccharide (LPS) derived from *Actinobacillus actinomycetemcomitans* (A. a.). We measured the level of prostaglandin E(2) (PGE(2)) production by DGF and NDGF by radioimmunoassay, and also measured the mRNA expression of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) by using the real-time PCR method. We found the higher levels of LPS-stimulated COX-2 mRNA expression and PGE(2) production in DGF when compared with those in NDGF. This study may indicate that overexpression of LPS-stimulated COX-2 induced a greater ability of DGF to produce PGE(2), and that these phenomena may be responsible for the severer periodontal disease in DS patients.

### **Homocysteine metabolism in children with Down syndrome: in vitro modulation.**

Am J Hum Genet 2001 Jul;69(1):88-95

The gene for cystathionine beta-synthase (CBS) is located on chromosome 21 and is overexpressed in children with Down syndrome (DS), or trisomy 21. The dual purpose of the present study was to evaluate the impact of overexpression of the CBS gene on homocysteine metabolism in children with DS and to determine whether the supplementation of trisomy 21 lymphoblasts in vitro with selected nutrients would shift the genetically induced metabolic imbalance. Plasma samples were obtained from 42 children with karyotypically confirmed full trisomy 21 and from 36 normal siblings (mean age 7.4 years). Metabolites involved in homocysteine metabolism were measured and compared to those of normal siblings used as controls. Lymphocyte DNA methylation status was determined as a functional endpoint. The results indicated that plasma levels of homocysteine, methionine, S-adenosylhomocysteine, and S-adenosylmethionine were all significantly decreased in children with DS and that their lymphocyte DNA was hypermethylated relative to that in normal siblings. Plasma levels of cystathionine and cysteine were significantly increased, consistent with an increase in CBS activity. Plasma glutathione levels were significantly reduced in the children with DS and may reflect an increase in oxidative stress due to the overexpression of the superoxide dismutase gene, also located on chromosome 21. The addition of methionine, folinic acid, methyl-B(12), thymidine, or dimethylglycine to the cultured trisomy 21 lymphoblastoid cells improved the metabolic profile in vitro. The increased activity of CBS in children with DS significantly alters homocysteine metabolism such that the folate-dependent resynthesis of methionine is compromised. The decreased availability of homocysteine promotes the well-established "folate trap," creating a functional folate deficiency that may contribute to the metabolic pathology of this complex genetic disorder.

### **Down Syndrome: Treatment and Care 1982.**

Schmid, F.

Aschaffenburg, Germany: Municipal Pediatric Clinic.

No abstract available.

### **Cell Therapy: A New Dimension of Medicine**

Schmid, F.

1983, p. 65. Thoune, Switzerland: Ott.

No abstract available.

### **[Studies on the state of vitamins B1, B2 and B6 in Down's syndrome] [Article in German]**

Schmid F, Christeller S, Rehm W.

Fortschr Med 1975 Sep 11;93(25):1170-2

In 110 children-between 0-16 years of age-, 90 children with Down-syndrome and 20 controls the following metabolic parameter were analyzed: ETK (vitamin-B1-activating coefficient), EGR (vitamin B2), P-5'-P, EGOT (vitamin B6), GOT, GPT, pH, K, Na, Ca, Cl, uric-acid (HS). Among some important correlations between the different parameters it could be demonstrated-for the first time to our knowledge-that in Mongoloids a disturbance of the vitamin-B1-metabolism exists, certified by the so-called transketolase-test.

### **Plasma carnitine levels in children with Down syndrome.**

Seven M, Cengiz M, Tuzgen S, Iscan MY. Genetik Arastirma Merkezi, Cerrahpasa Tip Fakultesi, Istanbul Universitesi, Cerrahpasa, Istanbul, Turkey. mehseven@istanbul.edu.tr

Am J Human Biol 2001 Nov-Dec;13(6):721-5

Carnitine is responsible for several chemical processes, including lipid metabolism, nerve cell conduction, reduction in muscle hypotonia, and limitation in oxidative damage to cells. In patients with Down syndrome (DS), the process of growth is behind that of normal children and neuromuscular control is attained somewhat later. The purpose of this study was to assess variation in levels of carnitine in normal and DS children and the relationship between the amount of carnitine and age. The study involved 30 (15 girls, 15 boys) normal children and 40 (20 girls, 20 boys) DS patients of Turkish ancestry, 6 months to 13 years of age. Carnitine level was

determined using Deufel's enzymatic method. Carnitine level was significantly lower in DS patients compared with normal children between 6 months to 5 years of age. Between 5 and 13 years of age, the level of carnitine was about the same in both the normal and DS groups. The results suggest that carnitine level shows a different pattern of age related increase in DS compared to normal children. Published 2001 Wiley-Liss, Inc.

### **Hearing loss in children with Down syndrome.**

Shott SR, Joseph A, Heithaus D. Department of Pediatric Otolaryngology, Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA. shots0@chmcc.org

Int J Pediatr Otorhinolaryngol 2001 Dec 1;61(3):199-205

**OBJECTIVE:** Previous studies report a 38-78% incidence of hearing loss in children with Down syndrome (DS). The purpose of this study was to establish more up to date information about hearing loss in children with DS. **METHODS:** A 5-year longitudinal study following the otolaryngologic problems seen in children with DS was initiated in February, 1999 at the Children's Hospital Medical Center in Cincinnati, OH. Aggressive, 'state of the art' treatment, both medical and surgical, was provided to a group of children, (n=48), all of whom were entered into the study at an age under 2 years. Specific interventions and treatments were reviewed in regards to following and treating the children's chronic ear disease. Hearing level results at the end of the first year of the study were evaluated in this publication. This includes both pre-treatment and post-treatment audiologic results. **RESULTS:** After treatment of easily reversible hearing loss from chronic otitis media, either with medical or surgical treatment with PET's, 98% of the children had normal hearing levels. Only two children had residual mild hearing losses after treatment interventions. **CONCLUSION:** Aggressive, meticulous and compulsive diagnosis and treatment of chronic ear disease in children with DS, started soon after birth, provides significantly improved hearing levels than reported previously.

### **Fluoride 1988; 2: 61-73**

Takahashi, K.

(<http://www.fluoride-journal.com/98-31-2/31261-73.htm>).

### **Thyroid dysfunction in children with Down's syndrome.**

Tuysuz B, Beker DB. Department of Paediatrics, Cerrahpasa Medical Faculty, University of Istanbul, Turkey. beyhantuysuz@yahoo.com

Acta Paediatr 2001 Dec;90(12):1389-93

Thyroid function tests were carried out on 320 children with Down's syndrome aged between 5 d and 10 y. Thyroid function was normal in 230 patients (71.9%) and abnormal in 90 (28.1%). Six patients (1.8%) had primary congenital hypothyroidism, one patient had acquired hypothyroidism and two had transient hyperthyrotropinaemia of the newborn. Sixteen of the remaining 81 patients (25.3%) had compensated hypothyroidism with increased thyroid-stimulating hormone (TSH) levels (11-20 mU l(-1)). Their T4 levels were found to be either normal or close to the lower limit of normal. These cases were started on thyroxine therapy. Sixty-five of the 81 patients had a mild compensated hypothyroidism with mild TSH elevation (6-10 mU l(-1)). None of the patients had hyperthyroidism. The antithyroid antibodies were positive in the acquired hypothyroidism case. Conclusion: The prevalence of congenital hypothyroidism was 1.8% in children with Down's syndrome while 25.3% of them had compensated hypothyroidism. It is suggested that Down's syndrome patients with normal thyroid functions and those with compensated hypothyroidism should be followed annually and every 3 mo, respectively. Besides congenital hypothyroidism cases, those with TSH levels between 11 and 20 mU l(-1) may benefit from treatment with low-dose thyroxine.

### **Dementia in people with Down's syndrome.**

Tyrrell J, Cosgrave M, McCarron M, McPherson J, Calvert J, Kelly A, McLaughlin M, Gill M, Lawlor BA. Department of Psychiatry, Trinity College Dublin, Dublin 2, Ireland. jfyrrel@tcd.ie

Int J Geriatr Psychiatry 2001 Dec;16(12):1168-74

**OBJECTIVES:** To determine the prevalence of dementia in an Irish sample of people with Down's syndrome (DS) and to examine associated clinical characteristics of dementia in this group. **METHOD:** 285 people with DS (Age 35-74 years, mean age +/- SD 46.5 +/- 8.2 years) were included in this cross-sectional study. The diagnosis of dementia was made using modified DSMIV criteria. Cognitive tests used were the Down's syndrome Mental Status Examination (DSMSE), Test for Severe Impairment (TSI) and adaptive function was measured by the Daily Living Skills Questionnaire (DLSQ). **RESULTS:** The overall prevalence of dementia was

13.3%. The presence of dementia was associated with epilepsy, myoclonus, and head injury. The demented DS group were significantly older (n = 38, mean age 54.7 years SD +/- 7.5) than the non-demented (n = 246, mean age 45.6, SD +/- 7.3). The TSI and DLSQ had a satisfactory spread of scores without 'floor' or 'ceiling' effects in people with moderate and severe learning disability. Median scores in demented versus the non-demented groups were significantly different for each measure of function. CONCLUSIONS: Dementia had a prevalence of 13.3% and occurred at a mean age of 54.7 years. The combination of DLSQ score, age and presence of epilepsy were found to predict presence of dementia. Copyright 2001 John Wiley & Sons, Ltd.

### **The use of 5-HTP in the treatment of Down's syndrome.**

Weise, P., Koch, R., Shaw, K.N., Rosenfeld, M.J.

Pediatrics 1974 Aug; 54(2): 165-8.

No abstract available.

### **Xylose absorption in Down's syndrome.**

Williams, Celia A. et al U Surrey, Div of Nutrition & Food Science, Guildford, England

Journal of Mental Deficiency Research 1985 Jun Vol 29(2) 173-177

Conducted a standard xylose absorption test in 14 25-61 yr old Ss with Down's syndrome (DS) and in 14 sex- and age-matched mentally retarded controls; another 30 14-57 yr olds with DS were similarly investigated. Mentally retarded Ss as a group had impaired xylose absorption, and the matched DS Ss had a significantly reduced xylose absorption when compared to the mentally retarded controls. It is suggested that the malabsorption plays a role in a number of the vitamin and mineral deficiencies found in people with DS.

### **Glutamine: from basic science to clinical applications.**

Ziegler TR, Szeszycki EE, Estivariz CF, Puckett AB, Leader LM. Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA.

Nutrition 1996 Nov-Dec;12(11-12 Suppl):S68-70

Glutamine (Gln) has been one of the most intensively studied nutrients in the field of nutrition support in recent years. Interest in provision of Gln derives from animal studies in models of catabolic stress, primarily in rats. Enteral or parenteral Gln supplementation improved organ function and/or survival in most of these investigations. These studies have also supported the concept that Gln is a critical nutrient for the gut mucosa and immune cells. Recent molecular and protein chemistry studies are beginning to define the basic mechanism involved in Gln action in the gut, liver and other cells and organs. Double-blind prospective clinical investigations to date suggest that Gln-enriched parenteral or enteral feedings are generally safe and effective in catabolic patients. Intravenous Gln (either as the L-amino acid or as Gln-dipeptides) has been shown to increase plasma Gln levels, exert protein anabolic effects, improve gut structure and/or function and reduce important indices of morbidity, including infection rates and length of hospital stay in selected patients subgroups. Additional blinded studies of Gln administration in catabolic patients and increasing clinical experience with Gln-enriched nutrient products will determine whether routine Gln supplementation should be given in nutrition support, and to whom. Taken together, the data obtained over the past decade or so of intensive research on Gln nutrition demonstrate that this amino acid is an important dietary nutrient and is probably conditionally essential in humans in certain catabolic conditions.

## DOWN'S SYNDROME

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- 

## **The value of screening for Down's syndrome in a socioeconomically deprived area with a high ethnic population**

Ford C.; Moore A.J.; Jordan P.A.; Bartlett W.A.; Wyldes M.P.; Jones A.F.; MacKenzie W.E.

Dr. C. Ford, Department Clinical Biochemistry, Birmingham Heartlands Hospital, Bordesley Green, Birmingham B9 5ST United Kingdom

British Journal of Obstetrics and Gynaecology (United Kingdom), 1998, 105/8 (855-859)

**Objective:** To assess the utility of biochemical antenatal screening for Down's syndrome in a socioeconomically deprived area with a high proportion of Asian women from the Indian Subcontinent.

**Design:** Audit of Down's syndrome biochemical screening service over a four-year period.

**Setting:** Teaching hospital and community antenatal clinic in inner city Birmingham.

**Population:** Women booked between October 1992, and December 1996.

**Methods:** Blood for screening was collected between 14 and 21 weeks gestation, alpha-fetoprotein and intact human chorionic gonadotrophin were measured in serum and the risk of Down's syndrome was calculated.

**Main outcome measures:** Uptakes of screening and amniocentesis, screen positive rate, odds of being affected given a positive result, miscarriages associated with amniocentesis offered following a high risk result, detection rate, number of Down's cases prevented and a cost analysis. Outcome measures were compared between Asians and Caucasians.

**Results:** Overall 11,974 women (71%) accepted serum screening. The screen positive rate was 8.3% in Asians and 5.0% in Caucasians. The uptake of amniocentesis in women following a high risk result was 54% overall (35% Asian, 67% Caucasian). Nineteen cases of Down's syndrome were identified, of which 13 occurred in women who opted for biochemical screening. The

detection rate of the biochemical screening program was 85% (11/13). Of these 11 cases, six (none of whom were Asian) elected to have an amniocentesis, of whom four thereafter had a termination.

Conclusion: In this study the public health benefits of screening for Down's syndrome in a socioeconomically deprived area with a high Asian population, were small.

## **Congenital disorders sharing oxidative stress and cancer proneness as phenotypic hallmarks: Prospects for joint research in pharmacology**

Pagano G.; Korkina L.G.; Brunk U.T.; Chessa L.; Degan P.; Del Principe D. ; Kelly F.J.; Malorni W.; Pallardo F.; Pasquier C.; Scovassi I.; Zatterale A.; Franceschi C.

G. Pagano, Italian National Cancer Institute, Fondazione G. Pascale, I-80131 Naples Italy  
Medical Hypotheses (United Kingdom), 1998, 51/3 (253-266)

In spite of very distinct genotypic assets, a number of congenital conditions include oxidative stress as a phenotypic hallmark. These disorders include Fanconi's anaemia, ataxia telangiectasia, xeroderma pigmentosum and Bloom's syndrome, as well as two frequent congenital conditions: Down's syndrome and cystic fibrosis. Cancer proneness is a clinical feature shared by these disorders, while other manifestations include early ageing, neurological symptoms or congenital malformations. The onset of oxidative stress has been related to excess formation, or defective detoxification, of reactive oxygen species (ROS). This can arise from either the abnormal expression or inducibility of ROS-detoxifying enzymes, or by defective absorption of nutrient antioxidants. Resulting oxidative injury has been characterized through: (i) DNA, protein or lipid oxidative damage; (ii) excess ROS formation (in vitro and ex vivo); (iii) sensitivity to oxygen-related toxicity; (iv) improvement of cellular defects by either hypoxia or antioxidants; and (v) circumstantial evidence for in vivo oxidative stress (as e.g. clastogenic factors). Investigations conducted so far have been confined to individual disorders. Comparative studies of selected indicators for oxidative stress could provide further insights into the pathogenesis of each individual condition. Such a unified approach may have wide-ranging consequences for studies of ageing and cancer.

## **Glucose effects on cognition in adults with Down's syndrome**

Manning C.A.; Honn V.J.; Stone W.S.; Jane J.S.; Gold P.E.

C.A. Manning, Department of Neurology, Box 394, Univ. of Virginia Hlth. Sci. Center, Charlottesville, VA 22908 United States  
Neuropsychology (United States), 1998, 12/3 (479-484)

Glucose enhances memory in a variety of individuals, including people with Alzheimer's disease. By 35 years of age, adults with Down's syndrome (DS) develop the characteristic plaques and tangles found in Alzheimer's disease, despite findings indicating that not all older DS individuals meet criteria for dementia. To examine the possibility that glucose enhances memory in adults with DS (mean age = 35 years, range = 19-55 years), adults with DS were given a battery of tests specifically designed for individuals with DS in glucose and control conditions. No participant met criteria for dementia, regardless of age. Glucose enhanced performance on tests requiring both long-term memory and auditory processing. In addition, increased age was associated with poorer performance on the majority of tests in the control condition, indicating that cognitive decline with aging may be more prevalent in DS than previously believed.

## **The influence of maternal weight correction formulas in Asian Down syndrome screening using alpha-fetoprotein and free beta- human chorionic gonadotropin**

Hsu J.J.; Hsieh T.T.; Soong Y.K.; Kuo B.

Dr. J.J. Hsu, Department Obstetrics and Gynecology, Chang Gung Memorial Hospital, 199 Tung-Hwa North Road, Taipei Taiwan  
Journal of Maternal-Fetal Investigation (United States), 1998, 8/2 (66-70)

Objective: To investigate the relationship between maternal weight and serum alpha-fetoprotein (AFP) and free beta-human chorionic gonadotropin (beta-hCG) levels and to determine the methodology of correction formulas for influencing the results of Down syndrome screening in an Asian population.

Methods: 8194 normal singleton pregnancies without any congenital anomalies were screened using AFP and free beta-hCG

between 14 and 22 weeks of gestation. Down syndrome risk was calculated by bivariate gaussian algorithm that combined information from the two biochemical measurements and maternal age. The all points regression method and median regression method were used to approach the study cases. Linear and quadratic regression correction formulas for AFP and free beta-hCG, either in analyte multiples of the median (MoM) or log analyte MoM, against maternal weight have been proposed in this study.

**Results:** The mean maternal weight is 54.95 plus or minus 7.36 kg in Taiwanese pregnant women during the second trimester. There is a distinctly inverse relationship between maternal weight and serum marker levels. The log quadratic regression correction formula was the most satisfactory equation fit to the distribution of both AFP and free beta-hCG levels with a wide weight range. Routine weight correction may have the small benefit of reducing the screen-positive rate 0.36% at the risk cut-off level of 1:270.

**Conclusions:** Maternal weight may affect the AFP and free beta-hCG levels. Although there is no discernible effect in maternal weight adjustment, it is worth making weight corrections for serum marker levels in order to reduce individual variance.

## **Rapid and simple prenatal DNA diagnosis of Down's syndrome**

Verma L.; Macdonald F.; Leedham P.; McConachie M.; Dhanjal S.; Hulten M.

Prof. M. Hulten, Molecular Medicine Research Centre, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL United Kingdom

Lancet (United Kingdom), 1998, 352/9121 (9-12)

**Background.** Prenatal diagnosis of chromosomal abnormality requires cytogenetic analysis of amniotic fetal cells. The necessary culture time delays diagnosis, is expensive, and requires substantial scientific expertise. In a masked prospective study, we investigated the feasibility of PCR amplification of chromosome 21 markers for the prenatal diagnosis of Down's syndrome.

**Methods.** The study population consisted of 2167 pregnant women, undergoing amniocentesis for prenatal diagnosis. In this cohort at least 1.5 mL amniotic fluid was available surplus to the requirements for traditional diagnostic methods. DNA was extracted from the surplus amniotic fluid and amplified in fluorescence-based PCR reactions, with three small-tandem-repeat markers located on chromosome 21. The products of the reactions were analysed on a DNA sequencer to identify the presence of two or three copies of chromosome 21.

**Findings.** In 2083 (97.4%) of 2139 samples of amniotic fluid that were not macroscopically blood-stained, two DNA markers gave an informative and correct result, identifying 2053 fetuses as normal and 30 as having trisomy 21 Down's syndrome (as confirmed by cytogenetic analysis). An extra marker was informative in 32 of 41 other clear samples. Thus a total of 99.6% informative results was achieved with these three markers. Macroscopically bloodstained samples (28 [1.3%]) were unsuitable for DNA testing. They gave a typical but non-informative result. There were no false-positive or false-negative results. **Interpretation.** The PCR-based DNA diagnostic test has great potential for improved prenatal diagnosis of Down's syndrome, with the advantage that results may be available within a day.

## **Atypical background somatic mutant frequencies at the HPRT locus in children and adults with Down syndrome.**

Finette BA; Rood B; Poseno T; Vacek P; Pueschel S; Homans AC

Department of Pediatrics, University of Vermont, Burlington 05401, USA.

Mutat Res (Netherlands) Jul 17 1998, 403 (1-2) p35-43

People with Down syndrome are 10-30 fold more likely to develop leukemia than the normal population. To date, little is known regarding the molecular mechanisms underlying this phenomenon. We have previously demonstrated that the spontaneous somatic mutant frequency (Mf) at a reporter gene, hypoxanthine-guanine phosphoribosyl transferase (HPRT), from a normal population showed a strict age dependency with an exponential increase in Mf from birth to late adolescents with a subsequent linear 2-5% increase per year in adults. In this study, we compared HPRT Mf in children and adults with Down syndrome using the HPRT T-cell cloning assay. We determined the Mf at the HPRT locus in 27 subjects with Down syndrome from ages 6 months to 53.4 years. Results demonstrated that background somatic Mf at the HPRT locus in children and adults with Down syndrome are not dependent on age as seen in a normal control population. Results also show that adults with Down syndrome have a significantly lower Mf than normal adults, and that children with Down syndrome have a significantly higher Mf than normal children, although the latter appears to be due to a decreased cloning efficiency (CE). These observations demonstrate that the frequency of spontaneous somatic mutations in children and adults with Down syndrome are atypical compared to normal controls, and suggest that the genetic mechanisms associated with background somatic mutational events in children and adults with Down

syndrome may be different.

## **Centromeric genotyping and direct analysis of nondisjunction in humans: Down syndrome.**

Shen JJ; Sherman SL; Hassold TJ

Department of Genetics and the Center for Human Genetics, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, OH 44106, USA.

Chromosoma (Germany) Jun 1998, 107 (3) p166-72

In species with chiasmata meioses, alterations in genetic recombination are an important correlate of nondisjunction. In general, these alterations fall into one of two categories: either homologous chromosomes fail to pair and/or recombine at meiosis I, or they are united by chiasmata that are suboptimally positioned. Recent studies of human nondisjunction suggest that these relationships apply to our species as well. However, methodological limitations in human genetic mapping have made it difficult to determine whether the important determinant(s) in human nondisjunction is absent recombination, altered recombination, or both. In the present report, we describe somatic cell hybrid studies of chromosome 21 nondisjunction aimed at overcoming this limitation. By using hybrids to "capture" individual chromosomes 21 of the proband and parent of origin of trisomy, it is possible to identify complementary recombinant meiotic products, and thereby to uncover crossovers that cannot be detected by conventional mapping methods. In the present report, we summarize studies of 23 cases. Our results indicate that recombination in proximal 21q is infrequent in trisomy-generating meioses and that, in a proportion of the meioses, recombination does not occur anywhere on 21q. Thus, our observations indicate that failure to recombine is responsible for a proportion of trisomy 21 cases.

## **Elucidating the mechanisms of paternal non-disjunction of chromosome 21 in humans.**

Savage AR; Petersen MB; Pettay D; Taft L; Allran K; Freeman SB; Karadima G; Avramopoulos D; Torfs C; Mikkelsen M; Hassold TJ; Sherman SL

Department of Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA.

Hum Mol Genet (England) Aug 1998, 7 (8) p1221-7

Paternal non-disjunction of chromosome 21 accounts for 5-10% of Down syndrome cases, therefore, relative to the maternally derived cases, little is known about paternally derived trisomy 21. We present the first analysis of recombination and non-disjunction for a large paternally derived population of free trisomy 21 conceptuses (n = 67). Unlike maternal cases where the ratio of meiosis I (MI) to meiosis II (MII) errors is 3:1, a near 1:1 ratio exists among paternal cases, with a slight excess of MII errors. We found no paternal age effect for the overall population nor when classifying cases according to stage of non-disjunction error. Among 22 MI cases, only five had an observable recombinant event. This differs significantly from the 11 expected events (P < 0.02, Fisher's exact), suggesting reduced recombination along the non-disjoined chromosomes 21 involved in paternal MI non-disjunction. No difference in recombination was detected among 27 paternal MII cases as compared with controls. However, cases exhibited a slight increase in the frequency of proximal and medial exchange when compared with controls (0.37 versus 0.28, respectively). Lastly, this study confirmed previous reports of excess male probands among paternally derived trisomy 21 cases. However, we report evidence suggesting an MII stage-specific sex ratio disturbance where 2.5 male probands were found for each female proband. Classification of MII cases based on the position of the exchange event suggested that the proband sex ratio disturbance was restricted to non-telomeric exchange cases. Based on these findings, we propose new models to explain the association between paternally derived trisomy 21 and excessive male probands.

## **The 'Severe Impairment Battery': assessing cognitive ability in adults with Down syndrome.**

Witts P; Elders S

S. Tees Community and Mental Health NHS Trust, Normanby, Middlesbrough, UK.

Br J Clin Psychol (England) May 1998, 37 ( Pt 2) p213-6

**OBJECTIVES:** To examine the utility of the 'Severe Impairment Battery' (SIB--Thames Valley Test Company) in assessing cognitive ability of adults with Down syndrome .

**DESIGN:** A within-subject repeated measures design was used to determine test-retest reliability of the SIB and the Vineland Adaptive Behaviour Scales (Interview Edition--Survey Form, 1984) were used to establish SIB criterion validity.

**METHODS:** Thirty-three adults with Down syndrome (from 152 known to an NHS Trust learning disability service) were selected on the basis of their or their carers' written consent. At the first administration of the SIB with the participant, a staff member completed a Vineland ABS. Thirty days later, the SIB was readministered to the participant.

**RESULTS:** Test-retest reliability of the SIB was high as was criterion validity determined by correlating SIB and Vineland ABS scores. Floor effects were not encountered.

**CONCLUSIONS:** The SIB can successfully be used with adults with Down syndrome to assess cognitive functioning over a wide range of ability and may be useful, if used longitudinally, in assessing for deterioration in cognitive functioning associated with dementia. Methodological limitations are discussed.

## **Prenatal diagnosis with use of fetal cells isolated from maternal blood: five-color fluorescent in situ hybridization analysis on flow-sorted cells for chromosomes X, Y, 13, 18, and 21.**

Bischoff FZ; Lewis DE; Nguyen DD; Murrell S; Schober W; Scott J; Simpson JL; Elias S  
Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas 77030, USA.  
Am J Obstet Gynecol (United States) Jul 1998, 179 (1) p203-9

**OBJECTIVE:** Currently, prenatal diagnosis of chromosome abnormalities requires invasive techniques such as amniocentesis and chorionic villus sampling that carry small but finite risks of fetal loss. A noninvasive approach is to isolate fetal cells from maternal blood by flow sorting followed by genetic interphase analysis with fluorescence in situ hybridization. Because the ratio of fetal to maternal cells is relatively low after flow sorting and to detect 90% to 95% of fetal aneuploidies associated with serious birth defects, a 5-color fluorescent in situ hybridization strategy is necessary for simultaneous detection of chromosomes X, Y, 13, 18, and 21 in all flow-sorted nuclei recovered from a specimen.

**STUDY DESIGN:** Fetal nucleated red blood cells were isolated from maternal blood in 40 cases (10.4 to 27.0 weeks' gestation) by flow cytometry on the basis of positive selection of CD71+ (transferrin receptor), CD45-, and LDS751 staining. Each case was evaluated for 5-color fluorescent in situ hybridization efficiency by determining the percentage of flow-sorted nuclei containing 8 hybridization signals for chromosomes X, Y, 13, 18, and 21.

**RESULTS:** A total of 42,312 flow-sorted nuclei from maternal blood samples were analyzed. In 5 of 16 (31%) cases with a male fetus, 0.16% of nuclei scored were identified as fetal by the presence of 1 signal each for chromosomes X and Y. Fetal trisomy 21 nuclei were accurately detected in 2 cases with a female fetus, each of which was subsequently confirmed.

**CONCLUSIONS:** Five-color interphase fluorescent in situ hybridization analysis can be used to effectively analyze rare fetal aneuploid nuclei in enriched flow-sorted cells isolated from maternal blood.

## **Adoption and fostering of babies with Down syndrome: a cohort of 593 cases.**

Dumaret AC; De Vigan C; Julian-Reynier C; Goujard J; Rosset D; Ayme S  
CERMES-INSERM U.304, Paris, France.  
Prenat Diagn (England) May 1998, 18 (5) p437-45

Recently, professionals in France have noticed an increase in newborns with Down syndrome (DS) being placed for adoption. The aim of this study was to investigate DS babies given up at birth for adoption and to consider the possible determinants of this in order to assess social acceptance of DS. A retrospective cohort of all living DS babies was collected from two birth-defect registries (Paris: 1981-1990; Marseilles area: 1984-1990). Follow-up data were collected: characteristics of the baby, biological parents and maternity units, age when given up for adoption, and type of foster care. The results showed that 19.4 per cent of infants with DS (115/593) were rejected by their parents. Multiple regression analysis indicated that foreign origin of the mother, area of residence, no associated major malformation, maternal age (15-24 years), and birth rank (> 2) variables were significantly associated with a lower placement rate. Among the 115 abandoned infants with DS, 88 came from unknown parentage (76.5 per cent). For half of them, adoptive placement (88/115) occurred before the age of 6 months. Socio-cultural attitudes play a great part in these family decisions. Equally important is the manner in which professionals propose adoption as an alternative to these parents of DS babies. They should be encouraged to consider all options before making a decision, so that the best solution can be found for the interest of all.

## **New triple screen test for Down syndrome: combined urine analytes and serum AFP.**

Bahado-Singh RO; Oz U; Kovanci E; Cermik D; Flores D; Copel J; Mahoney M; Cole L  
Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT 06520-8063, USA.  
J Matern Fetal Med (United States) May-Jun 1998, 7 (3) p111-4

In this study we report a new triple test that combines serum AFP, urine beta-core fragment of hCG, total urine estriol, and maternal age for calculating individual Down syndrome odds in the second trimester. The urine beta-core fragment/estriol ratio was used as a single screening variable. Analyte levels were measured prospectively in 10 Down syndrome cases and 346 normals. Individual Down syndrome odds were calculated by multiplying the product of the Down syndrome likelihood ratios of serum AFP and urine beta-core/estriol levels by the age-related midtrimester risk. The screening efficiency of an algorithm that combines urine beta-core/estriol with maternal age was compared to one that included serum AFP data. A 90% detection rate for Down syndrome was obtained at a 4.65% false positive rate. This was superior to the 75% sensitivity at 5% false positive rate observed when beta-core/estriol and age alone were used. This new triple test has a higher screening efficiency than that generally reported for the traditional serum triple screen and other urine tests, and it also provides information on the risk of neural tube defects. If confirmed in larger trials, the new algorithm could be used as an alternative to the traditional serum triple screen.

## **Evidence against the involvement of reactive oxygen species in the pathogenesis of neuronal death in Down's syndrome and Alzheimer's disease**

Hayn M.; Kremser K.; Singewald N.; Cairns N.; Nemethova M.; Lubec B.; Lubec G.  
Department of Pediatrics, University of Vienna, Wahringer-Gurtel 18-20, A-1090 Vienna Austria  
Life Sciences (USA), 1996, 59/7 (537-544)

It has been proposed that the pathogenesis of Down's Syndrome (DS) involves reactive oxygen species (ROS) arising from a gene dosage effect that disproportionately elevates superoxide dismutase (SOD1) activity. It was also suggested that generation of ROS might be responsible for neuronal death in Alzheimer's Disease (AD). Little data on brain ROS in DS and AD exist; therefore, we determined activities of choline acetyltransferase (CHAT) and of the oxidative defense enzymes SOD1 and glutathione peroxidase (GSHPx) in frontal cortex of aged patients with DS and AD. We also measured levels of malondialdehyde, which reflects lipid peroxidation, and o-tyrosine, which represents the hydroxyl radical attack. ChAT was significantly reduced in cortex of patients with DS (-68%) and AD (-66%) as compared to controls. There were no statistically significant differences, however, between controls and both neurodegenerative disorders for SOD1, GSHPx, malondialdehyde and o-tyrosine. Our data contradict the only previous finding on increased SOD1 and ROS in brains of patients with DS: age as well as methodological differences might account for the discrepancy. In conclusion, no evidence for a pathogenetic role of SOD1, GSHPx, lipid peroxidation or hydroxyl radical attack in aged patients with DS and AD could be provided.

## **Sequence of deposition of heterogeneous amyloid beta-peptides of APO E in Down syndrome: Implications for initial events in amyloid plaque formation**

Lemere CA, Blusztajn JK, Yamaguchi H, Wisniewski T, Saido TC, Selkoe DJ  
Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.  
Neurobiol Dis 1996 Feb;3(1):16-32

Patients with trisomy 21 (Down syndrome (DS)) progressively develop amyloid beta-protein (Abeta) deposits and then other features of Alzheimer's disease (AD) apparently due to increased gene dosage and thus expression of the beta-amyloid precursor protein. Because the neuropathological phenotype in older DS subjects closely resembles that of AD, the examination of DS brains of increasing age provides a unique model of the progression of AD. Here, we characterized the deposition of several Abeta peptides and apolipoprotein E in formalin-fixed brain sections from 29 DS subjects between 3 and 73 years old. Amyloid plaque number and the percentage of cortical area they occupied were quantified by computerized image analysis. Abeta ending at amino acid 42 (Abeta42) was the earliest form of Abeta deposited in DS cortex. It was observed in 7 of 16 young (3-30 years) subjects, with the earliest deposition occurring at age 12. Abeta ending at residue 40 (Abeta40) was not detected until similar age 30, a time when degenerating neurites around Abeta immunoreactive (IR) plaques were first observed, and the frequency of Abeta40 IR plaques then rose with age. Even in old (51-73 years) DS subjects, Abeta42 IR plaques were always more abundant than Abeta40 IR plaques. Abeta peptides starting at aspartate 1 or pyroglutamate 3 were detected in small subsets of compacted, neuritic plaques beginning around age 30 and rose with age, the latter species always exceeding the former. Thus, the N-termini of the Abeta42 peptides abundantly deposited in very young DS subjects remain unknown. Apo E was detectable in a small subset of

Abeta42 IR plaques beginning at age 12 and rose steadily with age; it clearly followed the deposition of Abeta. Our analysis of very young DS brains suggests that amyloid plaque formation begins with Abeta42-ending peptides, and the number and percentage of cortical area of Abeta42 plaques increase very little with advancing age, while other heterogeneous Abeta species and Apo E progressively accrue onto plaques containing Abeta42.

### **Vitamin E and Alzheimer's disease in subjects with Down's syndrome.**

Jackson, C. V.; Holland, A. J.; Williams, C. A.; Dickerson, J. W.  
U Surrey Div of Nutrition & Food Science, Guildford, England  
Journal of Mental Deficiency Research 1988 Dec Vol 32(6) 479-484

Tested the hypothesis that a low level of serum Vitamin E would be associated with a likelihood of dementia in 24 Ss (aged 30+ yrs) with Down's syndrome. Blood samples were drawn, and evidence of deterioration in self-care skills was assessed. Nine Ss showed evidence of Alzheimer's disease (AD), and 9 did not. Plasma Vitamin E levels measured in Ss with AD were lower than in Ss without AD. It is suggested that there may be an interaction between risk of AD and the protective action of Vitamin E.

### **Behavioral disorders, learning disabilities and megavitamin therapy.**

LaPerchia, Phyllis  
New York City Board of Education, NY, US  
Adolescence 1987 Fal Vol 22(87) 729-738

Reviews research on megavitamin nutritional therapy for learning disabilities in general, schizophrenia, autism, mental retardation and Down's syndrome, and hyperkinesia. Methodological problems in the studies are noted, and a holistic approach to treating the learning and behaviorally disabled is advocated.

### **Macrocytosis and cognitive decline in Down's syndrome.**

Hambidge, D. M.  
Princess Alexandra Hosp, Swindon, England  
British Journal of Psychiatry 1986 Dec Vol 149 797-798

Questions R. L. Welfare and K. E. Hewitt's (see PA, Vol 74:22330) proposal of a causal relationship between cognitive decline and macrocytosis in Down's syndrome, suggesting that both may be related to undetected folate vitamin deficiency.

### **Treatment approaches in Down's syndrome: A review.**

Foreman, Philip J.; Ward, James  
Newcastle Coll of Advanced Education, Australia  
Australia & New Zealand Journal of Developmental Disabilities

Reviews research into treatment approaches in Down's syndrome, including pharmacological therapy (e.g., thyroid treatment, 5-hydroxytryptophan (5-HTP), vitamin and mineral therapy, cell therapy), the G. Doman (1974) program of movement patterning, early intervention, and facial plastic surgery.

### **A double blind study of vitamin B-sub-6 in Down's syndrome infants: I. Clinical and biochemical results.**

Coleman, Mary et al  
Georgetown U School of Medicine  
Journal of Mental Deficiency Research 1985 Sep Vol 29(3) 233-240

19 infants with Down's syndrome participated in a double-blind study of the clinical effects of pharmacological doses of vitamin B-sub-6 administration, starting under 8 wks of age and continuing until 3 yrs of age. 10 Ss received the vitamin and 9 the placebo. No statistically significant differences were found between the 2 groups in mental age, height, weight, cranial circumference, or tongue protrusion. Vitamin B-sub-6 significantly elevated whole blood 5-hydroxytryptamine during the 1st yr. A study of side effects conducted on a larger open population of 400 Down's syndrome patients (from infants to aged 12 yrs) found vitamin B-sub-6 to be relatively safe when administered over long periods of time, with photosensitive blisters as the major complication.

### **A double blind study of vitamin B-sub-6 in Down's syndrome infants: II. Cortical auditory evoked potentials.**

Fragar, Joseph; Barnet, Ann; Weiss, Ira; Coleman, Mary  
Montefiore Hosp & Medical Ctr, Dept of Medicine, New York, NY  
Journal of Mental Deficiency Research 1985 Sep Vol 29(3) 241-246

Recorded cortical auditory evoked potentials (CAEPs) at 1 and at 3 yrs of age in 19 children with Down's syndrome participating in a double-blind trial of vitamin B-sub-6 and placebo that was begun in early infancy and continued for 3 yrs. CAEPs have previously been shown to have abnormally high amplitude in Down's syndrome patients. The CAEPs of the Ss in the B-sub-6-treated and placebo groups were compared. Only minor effects were found in the CAEPs recorded at 1 yr of age. At 3 yrs of age, however, comparison of the B-sub-6-treated group and the placebo group revealed significant differences in both amplitudes and latencies of CAEP components. Peak-to-peak amplitudes of prominent components were significantly lower in B-sub-6-treated Ss than in their placebo controls. Amplitude correlated in some cases with whole blood serotonin levels. Latencies for several prominent evoked peaks were significantly longer in B-sub-6-treated Ss. Findings suggest a difference in neurodevelopmental trajectories that seems to be a pharmacological effect of B-sub-6 administration. (17 ref)

### **Xylose absorption in Down's syndrome.**

Williams, Celia A. et al  
U Surrey, Div of Nutrition & Food Science, Guildford, England  
Journal of Mental Deficiency Research 1985 Jun Vol 29(2) 173-177

Conducted a standard xylose absorption test in 14 25-61 yr old Ss with Down's syndrome (DS) and in 14 sex- and age-matched mentally retarded controls; another 30 14-57 yr olds with DS were similarly investigated. Mentally retarded Ss as a group had impaired xylose absorption, and the matched DS Ss had a significantly reduced xylose absorption when compared to the mentally retarded controls. It is suggested that the malabsorption plays a role in a number of the vitamin and mineral deficiencies found in people with DS.

### **Nutritional aspects of Down's syndrome with special reference to the nervous system.**

Sylvester, Peter E.  
St Lawrence's Hosp, Caterham, England  
British Journal of Psychiatry 1984 Aug Vol 145 115-120

Reviews studies that demonstrate that patients with Down's syndrome (DS) are prone to suffer multiple deficiencies of vitamins and lifelong shortages of some trace metals. A significant reason for these deficiencies is malabsorption from the intestine. Reversal and control by treatment of vitamin deficiencies have been reported. The brain in DS does not develop adequately; one area, the hippocampus, which is concerned with memory, is poorly developed. A major neuropathological feature of DS is premature aging of the Alzheimer type. The incidence of aging based on pathological findings is demonstrated and compared with senile changes in adults with DS. The role of nutrients is discussed in relation to damage to the mature brain and to the aging process.

### **Children's mental retardation study is attacked: A closer look.**

Schauss, Alexander G.; Sommars, Elisabeth  
American Inst for Biosocial Research, Tacoma, WA  
International Journal of Biosocial Research 1982 Vol 3(2) 75-86

Discusses research done to determine whether nutritional supplements can help mentally retarded children. The research has come under the attack from the Committee on Nutrition of the American Academy of Pediatrics (AAP). R. F. Harrell (1981) reported that when her team took 22 developmentally disabled children and placed them on vitamin supplements called the G-T-C formula in a double-blind, crossover study during an 8-mo period, they were able to consistently cause a significant increase in all the Ss' IQs. Two ongoing studies in the area of mental retardation and nutritional supplements are discussed in an effort to determine attempts to corroborate Harrell's findings. In the 1st study, 60 Down's Syndrome schoolchildren (aged 7-14 yrs) are involved in a 6-mo preexamination stage in which they are undergoing a series of tests, including tests to detect thyroid problems. These tests have been chosen to disprove a criticism by the AAP that suggested improvement in the Harrell children may have been due to a correction in thyroid problem. In the 2nd study, 40 children with Down's Syndrome are being tested, with half the Ss receiving the G-T-C formula and the other half receiving placebos. It is concluded that there is much hope for children with developmental disabilities in nutritional studies that examine the possibility of brain regeneration.

### **Effects of nutritional supplementation on IQ and certain other variables associated with Down syndrome.**

Weathers, Caislin  
Georgia Mental Health Inst, Atlanta  
American Journal of Mental Deficiency 1983 Sep Vol 88(2) 214-217

In a double-blind study, 24 6-17 yr old Down's syndrome children (Iqs 30-67 at the start of the study) who were living at home were given a megadose multivitamin/mineral supplement for 4 mo. A matched group of 23 children received a placebo in identical form. Ss' IQ (Stanford-Binet Intelligence Scale), vision, and visual-motor integration (Beery-Buktenica Developmental Form Sequence) were tested before and after supplementation, and weekly checks were made to monitor behavioral changes. No differences were found on any measures as a result of supplementation. (10 ref)

### **Vitamin A and carotene values of institutionalized mentally retarded subjects with and without Down's syndrome.**

Barden, H. S.  
U Illinois  
Journal of Mental Deficiency Research 1977 Mar Vol 21(1) 63-74

Assessed vitamin A and carotene values of 44 3-34 yr old Down's syndrome, 56 3-35 yr old non-Down's syndrome mentally retarded, and 40 normal 1-25 yr old Ss. Dietary and environmental uniformity was maintained by utilizing Down's and non-Down's Ss residing in the same institution. Results show that Down's Ss showed vitamin A values that were significantly higher than those of the non-Down's retarded Ss and similar to those of the normal Ss. Carotene values were similar in the Down's and non-Down's retarded groups, but were significantly higher than those of the normal Ss. This difference in carotene is seen as reflecting in part the high level of carotenoid products in the institutional diet. Carotene/vitamin A ratio values are reported, and the possibility that relatively high ratio values reflected a decreased efficiency in converting carotene to vitamin A is discussed. It is suggested that Down's Ss may suffer some impairment in the utilization of vitamin A at its site of action.

### **Sodium-dependent glutamate binding in senile dementia.**

McGeer, Edith G.; Singh, Edith A.; McGeer, Patrick L.  
U British Columbia, Kinsmen Lab of Neurological Research, Vancouver, Canada  
Neurobiology of Aging 1987 May-Jun Vol 8(3) 219-223

Investigated sodium-dependent glutamate binding as a possible index of the integrity of glutamate/aspartate nerve endings in 7 cortical areas from postmortem brains of 15 persons with senile dementia of the Alzheimer type (SD); 10 controls matched for age, sex, and postmortem delay (PMD); and single cases of Down's syndrome and Parkinson-dementia. Results show that binding affinities were variable from brain to brain. Specific binding site densities showed overall a significant negative correlation with PMD, a significant decrease in SD, and a significant correlation in the SD samples with choline acetyltransferase activities.

### **Alzheimer-like neurotransmitter deficits in adult Down's syndrome brain tissue.**

Analyzed brain tissue taken at necropsy from 5 cases of Down syndrome and 6 controls for changes in neurotransmitter markers. Concentrations of noradrenaline (NA), dopamine and its major metabolite homovanillic acid, and 5-hydroxytryptamine (5-HT) and its metabolite 5-hydroxyindoleacetic acid were determined by high pressure liquid chromatography, while choline acetyltransferase (ChAT) was measured by a radiochemical technique. Significant reductions in NA, 5-HT and ChAT were found in most cortical and subcortical regions of the Down syndrome tissue. Neuropathological lesions were also assessed. Results indicate profound transmitter deficits and neuropathological abnormalities in adult patients with Down syndrome that closely resemble those of Alzheimer's disease.

#### **A report on phosphatidylcholine therapy in a Down Syndrome child.**

Cantor, David S.; Thatcher, Robert W.; Ozand, Pinar; Kumin, Libby et al  
U Maryland School of Medicine, Applied Neuroscience Research Inst, Baltimore  
Psychological Reports 1986 Feb Vol 58(1) 207-217

Presents the case of a 21/2-yr-old Downs syndrome (DS) boy who was given a phosphatidylcholine supplement (150 mg/kg, day) over a 7-mo period. Measures of the EEG indicate a normalization during the treatment period with minor reoccurrence of abnormalities during a placebo period. S showed a definitive increase in speech and language skills as well as general motor skills that exceeded same-aged DS peers experiencing like training programs. Data suggest that phosphatidylcholine therapy may be useful for improving neurophysiological and intellectual functioning of some DS children.

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