

Abstracts from the 2nd International Conference on Chromosome 21 and Medical Research on Down Syndrome: Part 2

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Scientific Advisor For The Conference: *National Down Syndrome Society (NDSS), New York, USA*

PRESENTATIONS

Otolaryngologic manifestations in Down syndrome - A five year study

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Otolaryngologic problems are frequently seen in children with Down syndrome (DS). This includes chronic ear infections and hearing loss, chronic rhinitis and sinusitis, and upper airway obstruction and sleep abnormalities. In February 1999, a 5 year study, following the ear, nose, and throat problems seen in children with Down syndrome began at the Children's Hospital in Cincinnati, Ohio. The purpose of this study is to develop a data base while providing the current 'state of the art' treatment, both medical and surgical, for the otolaryngologic manifestations of DS. By starting with only very young children, we hope to eliminate any secondary consequences that may occur from these conditions not being treated appropriately. The need for such a study comes from the belief that much of the current data is retrospective and uncontrolled. We hope to establish more accurate 'norms' and elevate the expectations of what this group of children can achieve. Too often in the past, the otolaryngologic problems were accepted as simply "part of the DS" and not aggressively addressed. There are currently 60 children enrolled. This presentation will review the study design as well as present preliminary data from the first 2 years of the study.

Influence of visual feedback information on a sequencing task in adults with Down syndrome

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The purpose of this study was to investigate the influence of visual feedback information on the acquisition of a sequencing task in adults with Down Syndrome (DS). 10 adults with DS and 14 normal adults performed a button pressing task in a specific sequence under the following

conditions: Full visual feedback (FVF)- button board fully visible with full view of their arm/hand. No visual feedback (NVF)- buttons on the board were visible and no visual feedback of their arm/hand. Hand feedback (HF)- buttons on the board visible and vision of the hand only. We compared mean speed of movement (MT) and mean reaction times (RT) between groups and across the 3 conditions. Interestingly, while no differences were observed in RT, significant differences were observed in MT in adults with DS across conditions. Movements were slowest in the NVF condition. HF decreased MT and FVF resulted in the shortest MT. Further analysis indicated that adults with DS who had a range of previous movement experiences performed similarly to the normal adults. These findings suggest that adults with DS rely on visual feedback when performing sequences of movement and practice in different environmental contexts may help to improve motor performance.

Identification and expression of genes in the Down syndrome critical region two: In search for the function of the DSCR2 gene

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Two complementary approaches have been followed to characterise the function of the novel gene DSCR2 (Down Syndrome Critical Region gene 2): the isolation and characterisation of the mouse gene homologue to the human DSCR2 gene, and the analysis of the expression of the gene in different human cell lines. The mouse cDNA has a length of 1012 bp and has a high homology to the human DSCR2 gene. The predicted mouse *dscr2* protein has an identity of 85.4% to the human protein, indicating that the DSCR2 protein has been conserved during the evolution. The *dscr2* gene is expressed throughout all the stages of the mouse embryo development. In adult mouse tissues, the gene is expressed in testis, kidney, liver, brain, heart, skeletal muscle, and pancreas. The levels of the DSCR2 mRNA correlate with cellular growth of T98G and Jurkat cells in response to different treatments. The expression pattern throughout the foetal development together with the cor-

relation observed with the cell cycle indicates a possible function for the DSCR2 gene related to cell proliferation.

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Usp25 located at 21q11.2 belongs to a new subfamily of deubiquitinating enzymes

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Deubiquitinating (UBP) enzymes are thought to play an essential role in protein degradation via the 26S-proteasome pathway. We have recently identified USP25, a specific-ubiquitin protease gene spanning over 150 kb at 21q11.2, a genuinely genepoor region of the human genome. Characterization of the homologous murine gene, mUSP25, allowed to obtain probes for expression analysis in mice. In situ hybridization assays on embryonic brains showed a clear correlation with proliferative neuroepithelial cells and postmitotic neurons. Moreover, a high level of expression was detected in the seminiferous tubules of adult mouse testis. In humans, Northern analysis revealed two USP25 transcripts, of approximately 4.6 and 6.5 kb, in most adult and foetal tissues, except in testis, where the highest level of expression and only one transcript of 4.6 kb was observed. Recently, data base homology searches and subsequent cDNA library screenings have allowed the identification of a new human UBP member, USP28, at 11q23. Genomic and protein sequence comparisons have suggested that USP 25 and USP28 constitute a new subfamily of UBP. Tissue-specific alternatively spliced products have been shown for both cytosolic enzymes. Although the ubiquitin system is essential to all eukaryotic cells and several deubiquitinating enzymes have been shown to contribute to development and differentiation, the specific function of most family members remains unknown. In our case, USP25 overexpression in Down syndrome foetal brains with respect to control samples would agree with the dosage effects described for other UBP members involved in aneuploidy syndromes, USP9X (DFFRX) in Turner syndrome and USP18 in DiGeorge syndrome, and with the in vitro data showing that either overexpression or inhibition of UBP leads to programmed cell death.

Transcriptome studies using DNA microarrays

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DNA microarrays are used to monitor changes in gene expression in response to any physiological, pathological or pharmacological variations. Microarrays containing 200 genes involved in neurotransmission (precursors for neuropeptides, enzymes involved in the synthesis of neurotrans-

mitters, calcium-binding proteins, subunits of receptors for neurotransmitters: glutamate, GABA, acetylcholine, serotonin, dopamine, adrenaline, somatostatin) were designed for mice, rat and human samples. In collaboration with various groups, we studied gene expression in brains of mice in which genes involved in neurotransmission were knocked out (KO). Because the KO animals appeared phenotypically normal with very slight behavioral modifications, we used the neurotransmission microarrays for studying compensations in gene expression. Results from a series of nine different KO will be presented. In the parvalbumin-calretinin and parvalbumin-calbindin KO mice several genes involved in GABAergic transmission are downregulated. Conversely in the KO for GABA-A receptor subunits calretinin and calbindin are downregulated. In addition we show on the GABA- α 2 KO mice that expression variations vary with the age of the animals and do not appear as constitutive variations. The DNA microarray technology has proven to be very useful in showing expression compensations on different transmission systems in KO mice. Recently brain samples from trisomic 16 mice (Ts1Cje) were applied to the neurotransmission DNA microarrays. Results show that genes that are present in three copies are overexpressed, together with other unexpected genes mapping to other chromosomes than chromosome 16.

Recombination across 21cen and chromosomal non-disjunction: Characterisation of new polymorphic markers on the short arm of chromosome 21

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Non-disjunction (NDJ) of chromosomes 21 during maternal meiosis is the major cause of trisomy 21. Altered recombination is the only known molecular correlate of NDJ, with half NDJ events being achiasmate and most remaining events presenting atypical location of recombination exchanges across the long arm of chromosome 21. In particular, an excess of peri-centromeric exchanges for meiosis II NDJ events has been evidenced using the most proximal polymorphic DNA markers available. We have sought to characterise more proximal markers on the long arm together with proximal markers of the short arm of chromosome 21 in order (i) to measure recombination frequencies across 21cen for normally disjoined chromosomes and for non-disjoined chromosomes, (ii) to determine unambiguously the meiotic stage of non-disjunction and (iii) to precise the relative importance of juxta-centromeric recombination in non-disjunction. Juxtacentromeric regions of chromosome 21 consist in a patchwork of intra- and inter-chromosomal genomic duplications, mainly present on other peri-centromeric regions of acrocentric chromosomes. Polymorphic markers embedded in these regions are therefore found in several copies in the genome. We will report our strategy and our progress on the characterisation of unique polymorphic markers in these regions and

Abstracts

our preliminary analysis of recombination activity across 21cen.

Calcipressin I is regulated at the transcriptional and post-translational levels by calcineurin

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Calcipressin I, encoded by the chromosome 21 gene DSCR1, is a calcineurin binding protein that belongs to the calcipressin family along with ZAKI-4 and DSCR1L2. Calcipressin I binds to calcineurin A, the catalytic subunit of the Ca²⁺/calmodulin dependent protein phosphatase PP2B, in a calcium independent way. The binding results in the inhibition of this enzyme. It has been previously described that dephosphorylation by calcineurin of specific conserved serine residues in the SP motives of the NFAT family members is responsible for their nuclear translocation. A similar SP consensus motif is present in all the members of the calcipressin family. In this sense, we have found that calcipressin I is a phosphoprotein. By mutation of the two serines of the SP motif we can predict that at least one of the two serines is phosphorylated. Finally, we have found that calcipressin I is also a substrate for calcineurin phosphatase activity. Since we have shown that calcineurin is also responsible for transcriptional activation of DSCR1, we can conclude that calcipressin I is regulated at two different levels by calcineurin, at the transcriptional and at the post-translational levels. DSCR1 is overexpressed in Down syndrome fetal brain. Although DS is a multifactorial disease, the role of the calcipressin I as an inhibitor of calcineurin signaling could provide new insights towards the possible involvement of this signaling pathway in the pathology of Down syndrome.

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DYRK1A (human minibrain) interacts with 14-3-3

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DYRK1A (MNBH) is a gene located on human chromosome 21q22.2. The enzymatic activity of the encoded protein product, DYRK1A, has been demonstrated in its orthologue Dyrk1A in rats: it is a dual specificity protein kinase, able to phosphorylate serine/threonine and tyrosine residues. However, the participation of DYRK1A or other DYRK-related kinases in a particular signal transduc-

tion pathway has not been yet elucidated. We have used the human full-length DYRK1A cDNA as a bait in the yeast two-hybrid system to screen a human fetal brain cDNA library. One of the interacting clones was found to encode the protein 14-3-3. The 14-3-3 proteins are a family of intracellular, dimeric, phosphoserine-binding molecules expressed in all eukaryotic cells that play important roles in a wide range of vital regulatory processes, such as mitogenic signal transduction, apoptotic cell death, and cell cycle control. We have generated deletion mutants of DYRK1A and determined the binding site for 14-3-3. Co-transfection of COS-1 cells with DYRK1A and 14-3-3 have shown colocalization of both proteins in DYRK1A characteristic nuclear speckles and in plasmatic membrane ruffles. Co-expression of DYRK1A and a dominant negative form of 14-3-3 has revealed an increased accumulation of DYRK1A, suggesting that 14-3-3 could be involved in the regulation of the half-life of DYRK1A.

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Enriched environment and behavioural performance of Ts65dn mice, a model for a Down syndrome: Gender differences

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We have assessed the effects of enriched environment (EE) upon behavioral and cognitive performances of partially trisomic Ts65Dn (TS) mice and their control (C) littermates. EE was applied to pups for 7 weeks after weaning. Circadian spontaneous activity (actimetry), exploratory behavior (hole board), total activity in the open field, passive avoidance behavior, and spatial memory (Morris water maze, repeated acquisition paradigm) were analyzed in 86 female and 75 male mice, starting 15 days after completing EE. For each gender, mice were distributed in non-EE and EE of C and TS groups. EE partially reduced in TS females and enhanced in TS males the circadian spontaneous activity. Exploratory behavior was increased by EE in all groups regardless of gender or presence of trisomy. Passive avoidance was modified by EE only in females, C and TS. In the Morris water maze, a significant improvement of the spatial memory was observed in EE-C female but not in EE-C male mice, as assessed by measurements of escape latencies and distances traveled. Performances in the 4 groups of C animals were also consistently and significantly better than those of the matching groups of TS mice. EE induced a significant improvement of performance in TS female animals. In contrast, EE deteriorated performance in TS male mice. In all groups, changes in escape latencies and distances induced by EE were accounted for by changes in the total time spent in the periphery of the pool. It is concluded

that EE may induce behavioral and learning changes in the TS mice, although the gender is a factor that play a modulatory role in the influence of EE. (Supported by Foundation 'Marcelino Botín', Real Patronato Atención Minusvalías, and SAF99-0092-C02-02).

Phenotypic characterization of a knockout mouse model for the *Dyrk1a/Mnbh* gene

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The human homologue (*DYRK1A/MNBH*) of the *Drosophila* minibrain (*mnb*) gene maps on 21q22.2. The *mnb* gene appears to play an essential role during postembryonic neurogenesis in regulating the number of distinct types of neuronal cells in *Drosophila*. In order to elucidate the functional role of the minibrain protein in mammals we have generated a knockout mouse for the *Dyrk1A/Mnbh* gene. These mice (*Mnbh*^{-/-}) are not viable and die between days 10 and 12 of embryonic development. Mice carrying a targeted disrupted allele (*Mnbh*^{+/-}) are viable and fertile. However, these mice are smaller in size than their wild type siblings and are born in a lower percentage than the expected one. Behavioral analyses indicate that the preweaning *Mnbh*^{+/-} mice present a developmental delay. Histological analyses show a reduction in the brain size of the *Mnbh*^{+/-} mice and minor differences in its general cytoarchitecture compared to their wild type littermates. These results indicate that the *Dyrk1A/Mnbh* gene acts in a dose-dependent manner. The lack of one copy of the gene causes an abnormal phenotype while the lack of two copies causes embryonic lethality.

Alzheimer's disease and Down syndrome clinical aspects and diagnostic guide-lines. Pharmacological treatment with donepezilo of the cognitive and behaviour damage in people with Down syndrome and Alzheimer's disease

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The study of ageing in people with intellectual disability is a recent subject of interest. Until a short time ago, living conditions for the majority of these people, irrespective of the gravity of their impairment, led them to premature death at an early age. There was little or no interest in their state of health, their adaptive competency and even less in changes made in accordance with the ageing process. As with the general population, the ageing of people with mental deficiency is a consequent circumstance of a combination of better health care and improved living conditions

that together increase life expectancy. Life expectancy in people with Down Syndrome has increased from less than 10 years of age at the beginning of the 20th century to 50 years of age now. In fact, around 20% of people with Down Syndrome can now live longer than 55 years. Age-related changes in people with Down Syndrome prompt us to suggest that these people age prematurely. Age-linked changes that can be observed in the general population from 70 years of age can be observed in people with Down Syndrome from the age of 30. Among other evidence, which reinforces this fact, can be seen a greater risk of sensorial, visual and hearing impairment, thyroid disorders and Alzheimer like dementia at an earlier age in people with mental deficiency when compared those to other etiologies. Down syndrome and Alzheimer's disease: Age-related changes in people with Down Syndrome are becoming of greater interest, especially because these persons develop at an early age neuropathologic damage typical of Alzheimer's disease. Neuropathologic studies have demonstrated that at the age of 30, several characteristics of Alzheimer's disease can be seen, such as amyloid defactation, senile plates, neurofibril balls, predominantly in the tonsils, the "hipocampo" and areas of cortical association in the frontal, temporal and parietal lobe. Neuropathologic damage is of special significance if we consider it in conjunction with early ageing indexes, reduction in life expectancy in people with Down Syndrome and evidence of the ever more outstanding relationship between Chromosome 21 genes and the development of Alzheimer's disease. Therefore, since deterioration in cognitive and behaviour functions is obvious, the anatomopathologic, neurophysiologic and neuroimaging findings suggest a great risk of developing on Alzheimer's disease from the 40's and 50's in a significant proportion of people with Down Syndrome.

Rationale for pharmacologic strategies to enhance cognition in Down syndrome

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The past two decades have witnessed unprecedented growth and development in the neurosciences. Several adult neurologic and psychiatric disorders, once considered untreatable, have become the targets of active biomedical intervention in an attempt to reduce impairment and improve function. Historically, there has been less interest within the biomedical community for making childhood cognitive disorders a legitimate priority for neurobiologic intervention. The prospect of pharmacologic treatment for cognitive impairment is frequently discussed and actively pursued by many families. Because these interventions are still in the development stage, recommendations for drug treatment are premature and cannot be routinely prescribed at this time. Since 1995, when many parents first became interested in giving Piracetam to their young children with Down syndrome, it became obvious that no research data was available regarding either safety or efficacy in this population. Piracetam is classified as a nootropic agent with demonstrated benefits on learning and memory in rodents. Human studies have been considerably less convincing. We

Abstracts

have conducted a small pilot study of Piracetam in 10 children with Down syndrome between the ages of 5-7 years. Two other classes of medicine also offer the potential for cognitive enhancement in persons with Down Syndrome: anti-cholinesterases, which increase the level of the neurotransmitter acetylcholine in the brain; and anti-amyloid compounds, designed to prevent or reduce the deposition of amyloid plaques in the aging brain. As new "cognitive medicines" are developed it is imperative that they be thoroughly and carefully tested to ensure safety and efficacy, especially in young children.

Celiac disease and Down syndrome

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Celiac disease is an autoimmune condition characterized by an immune mediated enteropathy of the small intestine. The condition occurs in genetically predisposed individuals who ingest gliadin and related proteins that are found in wheat, rye or barley. Celiac disease produces a spectrum of small intestinal mucosal changes (increase in the number of intraepithelial lymphocytes, flattening of the villi and crypt hyperplasia). Malabsorption of nutrients is a consequence of the intestinal damage, causing significant malnutrition when prolonged. Clinical symptoms of celiac disease differ considerably depending on the age at presentation. In children diagnosed within the first years of life intestinal symptoms (short stature, delayed puberty, anemia, enamel hypoplasia, osteopenia, etc). Celiac disease may also be clinically silent. Several serological tests are useful to identify individuals requiring intestinal biopsy for definitive diagnosis. The tests used measure antibodies to gliadin, reticulon, endomysium and tissue transglutaminase. Treatment of celiac disease requires lifelong adherence to a diet, complete recovery of the small intestinal damage can be expected with resolution of related symptoms.

The association between Down syndrome and celiac disease, although occasionally observed in the past, has been reported with increasing frequency during the last decade. Prevalence rates of celiac disease in patients with Down syndrome found in different studies range from 2.5 to 18.6%. These significantly higher prevalence rates of celiac disease in children and adolescents with Down syndrome found by different authors indicate that the coexistence of these disorders is not fortuitous. It has been suggested that there are common pathogenetic factors in these diseases, such as the presence of common histocompatibility (HLA) antigens probably involved in the immune response. There is a high prevalence of immune-related disorders in patients with Down syndrome. In patients with celiac disease, autoimmune disease are also reported. Common immunogenetic markers, particularly HLA antigens, have been discussed as a possible link for the association. The association between celiac disease and HLA-DQ2 haplotype (DQA1*0501 and B1*0201 alleles) has been clearly established.

In order to determine the real prevalence of celiac disease in Down syndrome, a large series of patients with trisomy 21 of our geographical area from different settings (hos-

pitals, special schools, occupational therapy centers) was studied. A total of 284 persons with Down syndrome aged between 1 and 25 years were included in the study. In all cases, serum concentrations of antigliadin antibodies (AGAs) (Pharmacia CAP system ELISA), antiendomysium antibodies (AEA) (indirect immunofluorescence) of IgA class or of IgG class in cases of IgA deficiency were determined. In all patients, a clinical study was made to evaluate the presence and time-course of symptoms related to celiac disease. Jejunal biopsy was offered to all patients with AEA positivity and to those with suggestive clinical manifestations of celiac disease. In 18 of the 284 subjects WITH Down syndrome, aged between 2 and 15 years, celiac disease was confirmed by jejunal biopsy. Accordingly, the minimum prevalence rate of celiac disease was of 6.3%. Ninety-four percent (17/18) and 78% (14/18) of patients with the association Down syndrome and celiac disease showed AEA and AGA positivity, respectively. Fifteen patients with the association celiac disease and Down syndrome (15/18) showed clinical manifestations compatible with celiac disease, with a predominance of intestinal symptoms (8/18) over those with atypical or extra-intestinal forms (7/18). Three patients had clinically silent forms of celiac disease (3/18). In conclusion, celiac disease should be included among the conditions related to Down syndrome. Measurement of serum concentrations AEA (or autoantibodies against tissue transglutaminase) should be added to the list of screening tests for celiac disease in patients with Down syndrome, otherwise definite association between both diseases may pass unnoticed and diagnosis of celiac disease considerably delayed.

Down syndrome and autism spectrum disorder, research on the dual diagnosis

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It is often thought that children with Down syndrome who also have characteristics of autism spectrum disorder are manifesting these patterns secondary to severe or profound mental retardation. We are beginning to understand that many of these children do meet diagnostic criteria for autism spectrum and the occurrence of the dual diagnosis is not rare. The Down Syndrome Clinic in Cincinnati reports an incidence of 6% diagnosed using the DSM-IV criteria for Pervasive Developmental Disorder/Autism. It is important for the professional community to better understand children with this dual diagnosis in order to focus on effective medical and therapeutic interventions. Developing research protocols that combine information developed by scientists working in the fields of autism and Down syndrome research will be vital to our success in better understanding the complexity of this group of children. A recent study did this by evaluating prolonged EEG's in children with Down syndrome and autism spectrum disorder. The results were consistent with what is reported in the literature related to EEG findings in children with autism. Twenty percent of the children with dual diagnosis had epileptiform abnormalities on EEG's without a history of clin-

ical seizures. Early recognition and diagnosis of autism in children with Down syndrome has significant implications for both the family and the professionals working with the child. It is important to understand the needs of the child in regards to therapeutic, educational and medical evaluations and interventions. Continued research is needed in this area to explore environmental and familial risk factors, MRI findings, biochemical changes and the role of the extra chromosome and its genes. Research can help us gain a better understanding of Down syndrome and autism spectrum disorder which will reduce barriers to diagnosis and improve access to appropriate medical and educational interventions.

Sleep disorders in patients with Down syndrome

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Sleep disorders have important impact on the quality of waking life for children and adolescents. Patients with Down syndrome are a risk group for disturbed breathing during sleep due to their structural characteristics affecting upper airway size. Children with attention deficit disorders show sometime behavior disorders that can be related to sleep pathology. The aim of the study is to know the existence of sleep disorders on patients diagnosed as having a Down syndrome and their repercussion over wake time.

Material and Method: Three pages screening questionnaire was administered to parents of Down syndrome patients and for comparison siblings of patients Down syndrome. The questionnaire included 14 items that focused on medical and structural characteristics, 12 items related to sleep behavior and 7 items related to daytime behavior.

Both groups results were compared and showed significant statistical differences.

Plasma amyloid beta protein 1-42 (A 42) levels are increased in old Down syndrome (DS) but not in young DS

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All adults with DS have neuropathological changes characteristic of Alzheimer disease (AD) by 40 years of age. Soluble forms of A generated from amyloid precursor protein commonly end at C-terminal residue 40 or 42. The possession of two variants of ApoE 4 allele is a significant risk factor for the development of AD. Our objective was to quantitate the levels of A 40 and A 42 in plasma from young DS (<40 years of age), old DS (>40 years) and age-matched normal controls, and analyze the relationships with apolipoprotein E (ApoE) phenotype. Blood was collected from 28 young DS (mean age SD years; 30.6) (5

with ApoE 4 allele and 23 without), 28 aged-matched controls (7 with ApoE 4 allele and 21 without), 32 old DS (51.7 years) (9 with ApoE 4 allele and 23 without) and 32 age-matched controls (10 with ApoE 4 allele and 22 without). A 40 levels were higher in young DS than controls ($p < .0001$). A42 levels in young DS and controls were similar. A 40 and A 42 levels were higher in old DS than controls ($p < .001$). There was no relationship between A levels with ApoE 4 allele in DS and controls. Plasma A42 is increased in old DS concurrently with the development of AD neuropathology.

Alopecia areata in children with Down syndrome

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Alopecia areata is a complication in children with Down syndrome being observed with a higher incidence than in the general population. Some of the resumed etiologies are vitamine A and zinc deficiency and hypothyroidism, but most of the cases are considered to be an autoimmune disorder. Among the 731 patients of our Preventive Medicine Clinic for children with Down Syndrome (children up to the age of 18 years) 17 (2.3%) had episodes of alopecia areata. Causative factors could be found in two (sequelae of the treatment of lymphoblastic leukemia and celiac disease, respectively), in 15 patients there were no apparent etiologic mechanisms. Nevertheless, 13 children were successfully treated (1 with celiac disease by a gluten free diet and 12 by homeopathic treatment).