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Intellectual Disability and Cognitive Impairment in Down Syndrome. From Birth to Old Age☆

Discapacidad y Deterioro Cognitivo en la Persona con Síndrome de Down. Del nacimiento a la vejez

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Cognitive Development, Behavior, and Socialization in People with Down Syndrome: Weaknesses and Strengths. The Child with Down Syndrome

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Cognitive development, behavior, and socialization reflect the complex process whereby the brain matures and learns. Since the brain is the least mature organ at birth, human individuals in their early years must rely on the environment for the necessary care and stimulation that will enable them to gain independence and develop their capabilities to the utmost. Children attain 85% of their adult head circumference in the first 5 years of life. This fact underscores the importance of the many changes that occur in those early years, laying the foundation for the future.

It should be clearly understood that overstimulation neither enhances nor accelerates neurological development; on the contrary, it may cause delay. Understimulation, on the other hand, has a negative impact on brain maturing. Stimuli need to be tailored to the child's developmental stage and must be embedded spontaneously and continually in the activities of daily living. Bath times, dressing times, and mealtimes, for instance, can serve as opportunities to work on quality of attention skills, eye contact, imitation responses, or associative responses.

We must highlight the fact that the family environment experienced in the early years of development is just as important for children with Down syndrome (DS) as it is for children without DS. By identifying the weaknesses and strengths of a child's individual, household, school, and social settings, it becomes easier to plan strategies that can enable that child to reach full potential. Family guidance and support provided by a team of specialists, including psychologists, speech therapists, educationalists, and others, is a key component of this process.

The Adult with Down syndrome

Dr. Antonia M.W. Coppus

Epidemiologist and specialist in people with intellectual disabilities in the Netherlands

Because of advances in care and medical treatment, there has been a steady improvement in the life expectancy and quality of life for persons with Down syndrome (DS). It is not known if the increase in longevity will also mean a delay of the age of onset of age-dependent diseases.

Methods: A prospective longitudinal DS study cohort was developed, consisting of participants of an outpatient clinic for adults with DS. In this clinic a yearly multi-disciplinary DS Health Watch program is provided. Since the inception, 150 participants have agreed to participate in a longitudinal prospective study. They have visited the outpatient clinic annually from 2007 to 2015, a mean follow-up of about 5 years (0.1–8.4 years).

Results: Findings include the most common health problems identified and those considered as risk factors associated with or aggravating dementia. These results show

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a discrepancy in health conditions between those in the younger and older age categories.

Conclusion: Accelerated aging and increased risk for Alzheimer's disease are characteristics of persons with Down syndrome and it is important to understand the factors that contribute to these risks.

Aging in a Person with Down Syndrome

Dr. Anne-Sophie Carret-Rebillat

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Life expectancy has increased considerably over the past few decades for people with intellectual disabilities, but health problems, along with their psychological and social repercussions, become more common as people grow older. Dementia is highly prevalent among adults with intellectual disabilities, particularly those with Down syndrome. Preservation of these patients' quality of life and wellbeing demands an awareness of their comorbidities and tailoring of care. The most widespread age-related conditions are hypothyroidism, obesity, epilepsy, sleep apnea, sensory impairments, and dementia. These conditions are frequently diagnosed and treated late, typically on a separate basis rather than using a whole-person approach, compounding the existing disability. Educators and care providers need training to recognize the symptoms, which frequently take the form of psychological and behavioral changes. Caring for these patients requires a baseline assessment of their intellectual disability when they reach an adult age; regular and tailored medical follow-up to prevent comorbidities, screen for them, and treat them; and training and support for their families and teachers.

Down Syndrome and Alzheimer Disease

Dr. Rafael Blesa

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Down syndrome (DS) is one of the genetic causes of Alzheimer disease (AD), according to the 2014 International Working Group criteria. Life expectancy has grown exponentially for people with DS in the past 30 years, so that 30% of this population is currently above 40 years of age. Symptoms of dementia in DS typically begin in a person's 30s, and affect up to 80% of people with DS by the age of 60 years. Early symptoms include memory lapses, language difficulties, and changes in personality and behavior. Other symptoms may include epileptic seizures, sleep disorders, and changes in gait. People with DS have an additional copy of the amyloid beta precursor protein (*APP*) gene, which leads to abnormal deposits of amyloid-b in the brain and is the main factor for the development of AD in DS (AD–DS). Gene polymorphisms associated with late-onset AD (including *APOE*E4*, *PICALM*, and *SORL1*) may also play a role in pathogenesis, speeding up the course of AD–DS and bringing forward the age of symptom onset, and other genes involved in neurodevelopment and neural function, such as *DYRK1A*, may contribute to the neurodegenerative process in AD–DS. Trisomy 21 also determines other abnormalities that may contribute to AD–DS either directly or indirectly, including altered cholesterol metabolism and immune system dysfunction. AD–DS is a very early-onset form of AD that places a massive burden on family members and on society, given the interplay of disability and dementia. It is currently taking on pandemic proportions as the baby-boomer generation ages, with prevalence at 80%. As an amyloid-mediated model of genetic AD which brings forward pathological changes and onset of symptoms, DS–AD is driving research into the pathogenetic mechanisms of AD, the diagnostic role of biomarkers, and the assessment of the effects of different types of treatment, particularly at the preclinical stage and especially where the aim is to prevent deposition of amyloid-b in the brain. DS needs to be addressed through a comprehensive healthcare plan, and the social needs created by DS–AD at every stage in its course must now unavoidably be taken into account, as they compound the need for healthcare and welfare resources experienced by people with DS and their families from infancy.

Down Syndrome: A Personal and Scientific Perspective

Dr. Jesús Flórez Beledo

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The presence of Down syndrome in the world we live in is inextricable from our biology as a species, with intrinsic frailty as its perennially ingrained characteristic. Human frailty and human dignity are one: they are so tightly intertwined that none of the implications of human frailty can detract one iota from human dignity. Thus, we approach Down syndrome, not as an abstract entity involving weaknesses and strengths given in averages or percentages, but as a material fact within the specific frame of an individual person who has both capabilities and limitations. Such a person is, by definition, my brother or my sister: a fellow member of my own species, with the same rights and duties as myself, adjusted to his or her own real possibilities.

Science can shed light so that we may learn and understand the effects of a particular type of frailty—effects, lest we forget, both good and bad. In this case, the frailty derives

from the threefold presence of genetic material associated with chromosome 21. Science provides increasingly reliable clues allowing us to delve further into the vast and arcane secrets of biology, which appears increasingly complex as it unfolds and therefore increasingly intriguing.

But learning more about Down syndrome carries a sting sometimes, when it forces us to confront a blunt reality that is frequently and unfortunately disguised and concealed. ''You have to make it look good,'' urge our marketing professionals; and so everything is hunky dory, pretty and lovely, simple as pie, nothing amiss. ''They're just slower,'' runs one of the lies.

But greater knowledge is not, in fact, a dangerous thing. Rather, it helps us avert risks, and lets us find more and better solutions when the ones we've been using fall short, or simply don't work. Only knowledge can provide a solid foundation for our actions and service: knowledge is the true basis of our hope. Fantasies, bromides, and white lies ultimately amount to deceit; and deceit is the breeding ground of failure, which leads to hopelessness and frustration.

Life has placed a person with Down syndrome by our side and in our care. That is our call to action. It must be heeded. It is demanding. It requires commitment. Our call to action is a child, a relative, a student, a patient, an employee, a neighbor. We must answer our call openly and resolutely, in the spirit of a true calling, in the noblest and richest sense of the word. We must commit firmly to help that one person develop, and eventually live as an adult, whatever their present age, by following the lines of action suggested by knowledge. With silent, patient, active, steadfast, resilient enthusiasm. There will, of course, be times of dejection and hurdles to overcome. Only through our personal transformation can we gradually, steadily, bit by bit, come to change social attitudes. There lies our challenge. Let us accept it and rise up to it, as our children require and demand.

Cognitive Impairment in People with Down Syndrome

Ms. Bessy Benejam

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There is a very close relationship between Down syndrome and Alzheimer disease owing to an overexpression of the gene for the amyloid beta precursor protein (APP), which is located in chromosome 21 and thus tripled in people with Down syndrome. The clinical diagnosis of Alzheimer-type dementia relies chiefly on observation and on cognitive test results. It is no simple task to recognize the changes in cognitive functioning and adaptive ability associated with the onset of Alzheimer-type dementia in people who have an intellectual disability, as most such changes are often attributed to the disability itself. In addition, the tests routinely used for the general population are not suited to detecting changes in the cognitive functioning of a person with an intellectual disability, particularly in the early stages of dementia. This presentation will discuss existing evidence regarding the most frequent neuropsychological manifestations and behavioral changes observed in people with Down syndrome who develop Alzheimer disease.

Behavioural and Psychological Symptoms of Dementia in Down Syndrome: Early Indicators of Clinical Alzheimer's Disease?

Dr. Peter Paul DeDeyn

Scientific Director of the Institute Born-Bunge at the University of Antwerp. Scientific Director of the Alzheimer Research Center at the University of Groningen, The Netherlands. Editor-in-Chief of Clinical Neurology and Neurosurgery

Behavioural and Psychological Symptoms of Dementia (BPSD) are a core symptom of dementia in addition to cognitive decline and impaired activities of daily living, and are extensively studied in patients with Alzheimer's disease (AD) in the general population. BPSD are associated with patient suffering, earlier institutionalization and accelerated cognitive decline, increased caregiver burden, and higher financial costs. Despite the high risk for Down syndrome (DS) individuals to develop dementia, BPSD have not been comprehensively assessed in the DS population. Due to the great variety of DS cohorts, diagnostic methodologies, sub-optimal scales, covariates and outcome measures, it is unlikely that BPSD have always been accurately assessed. However, accurate recognition may increase awareness and understanding of these behavioural aberrations, thus enabling adaptive caregiving and, importantly, allowing for therapeutic interventions. Particular BPSD can be observed (long) before clinical dementia diagnosis and could therefore serve as early indicators of those at risk, and provide a new, non-invasive way to monitor, or at least give an indication of, the complex progression to dementia in DS. Strikingly, not a single behavioural assessment scale has been adapted and validated for AD in DS, thus not taking the DS-specific circumstances into account. Together with Dutch and European partners, we are developing a novel evaluation scale for BPSD in DS. Here, a summary of the rather limited knowledge on BPSD in DS will be presented (Dekker et al., 2015), as well the first phase of scale development, and the importance and potential of accurate recognition of BPSD in DS for daily clinical practice.

Diagnostic Criteria: The Diagnosis of Cognitive Impairment in a Person with Intellectual Disability

Dr. Andre Strydom

Reader in Intellectual Disabilities at University College London's Faculty of Brain Sciences (Division of Psychiatry) and a Consultant Psychiatrist in Developmental Disabilities. Chief investigator of the LonDownS consortium

The presentation of dementia in individuals with intellectual disability (ID) and with Down syndrome (DS) differs from typical Alzheimer's disease (AD), which affects how clinicians diagnose dementia in this population. Diagnostic issues will be reviewed as well as results from studies that have compared clinical diagnoses of dementia against manualised criteria, including the International Classification of Diseases (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) dementia criteria as well as the new DSM-5 criteria for neurocognitive disorder. Implications for diagnostic and outcome measures in clinical studies will be discussed, with a particular focus on DS.

Basic Research on Down Syndrome

Dr. Mara Dierssen

Doctorate in Neurobiology from Universidad de Cantabria, Spain. Cell and Systems Neurobiology group within the Systems Biology program at the Barcelona Centre for Genomic Regulation. Member of the European Academy and of the Dana Alliance Co2 for the Brain

Down syndrome (DS) is the main cause of intellectual disability and the most common genetic disorder in humans. Recent years have seen significant progress in terms of conceptual knowledge and clinical management of neuropathological features of DS, largely thanks to new discoveries in genomics and epigenomics, technological developments in basic neuroscience, and advances in neuroimaging, which has burst into the scene in both basic and clinical research.

Many lines of research are attempting to identify which of the tripled genes present in DS contribute the most to its peculiar neuropathological features. However, the contribution of noncoding parts of the genome to the phenotype also needs to be understood. There is increasing evidence that the pathophysiology of intellectual disability is caused by impaired experience-dependent neuroplasticity, which hampers the adaptation of synaptic function to environmental change. Our increased knowledge of pathophysiology has paved the way for clinical trials of drug therapies to improve cognitive performance, although most treatment approaches focus on early intervention. We must therefore pause to consider in depth our existing intervention programs developed over the years, to bring on board new information relevant to their content and their implementation. Issues pertaining to family life, integration at school and in the workplace, and implementation in specific communities all need to be considered in this process.

Clinical Experience with Down Syndrome at Fundació ACE

Dr. Isabel Hernández

Neurologist. Clinical chief at Fundación ACE. Coordinator of the Cognitive and Behavioral Disorder Diagnostic Unit. Head of clinical care for the Fundació ACE Day Care Services. Principal neurologist for Down syndrome patients at the Diagnostic Unit

People with Down syndrome have a higher-than-average rate of dementia, with clinical onset also occurring earlier. The triple genetic dose of Down syndrome leads to an increased susceptibility to Alzheimer disease.

Histopathologically, the brains of people with Down syndrome and dementia have the same type of lesions as patients with Alzheimer disease; however, the same cannot be said of their clinical presentation.

Neurologists who specialize in neurodegenerative diseases and are accustomed to diagnose dementia by assessing cognitive skills and functioning find it difficult to determine whether a person with Down syndrome has progressive cognitive impairment, given the medical specificities of the syndrome and the degree of intellectual impairment already present.

Dementia cannot be objectively assessed in people with Down syndrome using the standards commonly employed for the general population: cognitive scales need to be adapted, and functional information provided by relatives, guardians, and/or occupational therapists needs to be given much more weight. Detailed history taking is therefore essential.

Thanks to new advances in the identification of biomarkers for Alzheimer disease, it is now possible to objectively determine whether a person with Down syndrome who has suspected progressive cognitive impairment actually has Alzheimer disease. However, biomarker tests are not readily available for daily clinical practice.

During this session I will discuss the experience of Fundació ACE regarding the diagnosis and treatment of dementia in people with Down syndrome, as well as the follow-up and support provided to patients and their families.

A New Integrated Health Plan for Adults With Down Syndrome in Catalonia

Dr. Juan Fortea

Neurologist specializing in behavioral neurology and dementias. Researcher at the Memory Unit in Hospital de la Santa Creu i Sant Pau, Barcelona. Coordinator of the Alzheimer and Down Syndrome Unit at Fundació Catalana de Síndrome de Down, Barcelona

Introduction: Down syndrome (DS) is associated with many medical complications. The complications experienced in adulthood, particularly Alzheimer disease (AD), need to be addressed because life expectancy is now significantly extended for people with DS. Fundació Catalana de Síndrome de Down (FCSD) and Hospital de Sant Pau have jointly developed a health plan for adults with DS that includes regular assessments for AD and other DS-associated comorbidities.

Methods: Sphere of operation: FCSD and Hospital de Sant Pau. Target population: People with DS aged 18 years and older, living in Catalonia. Procedures: Standardized medical, neurological and neuropsychological assessment at

the FCSD's Down Medical Center; electroencephalography; and laboratory tests. Patients with medical or neurological disorders are to be referred to a tertiary care hospital for specific treatment. Patients will be offered the chance to participate in an intensive research program looking into biomarkers.

Results: We will present the results of the first year of implementation and analyze the prevalence of various comorbidities, with a particular emphasis on neurological disorders and on AD, specifically. We will also present preliminary findings from the linked research program.

Conclusions: AD is the chief health problem of adults with DS. Early detection and treatment of this condition requires a health plan that includes longitudinal follow-up. We have built an integrated health plan around this core, and developed an intensive research program to examine biomarkers of AD.

Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) Project

Ms. María Carmona Iragui

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Objectives: Most patients with Down syndrome (DS) develop presenile onset Alzheimer disease (AD). The natural history of AD and AD related biomarkers in DS remain unclear. We have developed a research initiative to periodically assess adults with DS. We present the first preliminary results of the program.

Methods: Subjects already assessed in the Down Medical Centre within the health plan for an early detection of AD. Subjects are proposed to undergo a cerebrospinal fluid (CSF) study to determine AD biomarkers, a magnetic resonance imaging (MRI), a positron emission tomography (PET) with amyloid tracer, a F18-deoxiglucose (FDG) PET, and a polisomnogram.

Results: So far, a CSF study was performed in 58 subjects with DS (median age: 47.5, 61.1% males), 33 of them demented. Forty underwent an MRI, 12 and 16 had also an amyloid and FDG-PET, respectively. A polisomnogram was performed in 28 subjects.

Preliminary results show abnormal levels of CSF biomarkers in more than 85% of the subjects. They all correlate with age. The structural MRI analyses reflect an accelerated aging of DS brains with atrophy affecting the same areas as AD does. Florbetapir PET was positive for amyloid retention in 8/12 patients, FDG-PET was abnormal in 7/16 patients. Polisomnography revealed several unnoticed sleep disturbances.

Conclusion: The DABNI program will provide insights into the natural history of AD and AD related biomarkers in DS and will enable a better and earlier AD diagnosis in the DS population. Our first preliminary results are in agreement with the recent conceptualization of DS as a form of preclinical AD.