ACADÉMIE NATIONALE DE MÉDECINE

Down Syndrome World Day

Press Release of the French National Academy of Medicine

March 19, 2021

The day of" March 21 has been chosen to symbolize Trisomy 21 (03/21, 3 chromosomes 21) and raise the public awareness of this congenital chromosomal anomaly, the leading cause of intellectual deficiency of genetic origin. This day, proposed in 2005 by the French Association for Research on Down Syndrome, was recognized as Down Syndrome World Day by the World Health Organization on December 20, 2007, then by the UN General Assembly on December 19, 2011[1]. Every year, events are organized around the world to defend the rights, inclusion, health and well-being of people with Down's syndrome.

The incidence of Down's syndrome is close to 1 / 2000 alive child births. Its prevalence is increasing due to the extension of life expectancy of people with Down's syndrome: currently about 70,000 in France. It is classified as a rare disease (ORPHA: 870). In addition to intellectual disability of varying intensity and constant physical manifestations (facial dysmorphia, muscular hypotonia, ligament hyperlaxity), people with trisomy 21 have an increased risk of cardiac malformations (atrio-ventricular duct), digestive malformations (duodenal atresia), ocular malformations (glaucoma, cataract). Language disorders are associated with deformities of the oral sphere, which impede pronunciation and impairs verbal communication. Some comorbidities are present in Down syndrome, such as acute megacaryoblastic leukemia recognized as a rare disease (ORPHA: 99887), autism spectrum disorders, obesity, diabetes, hypothyroidism, premature aging and Alzheimer's disease. The incidence of solid tumors is low. The pathologies associated with Down's syndrome vary by subject and age. The study of comorbidities can shed light on the role of pleiotropic genes in Down syndrome in comparison with the general population. People with Down's syndrome have been found to be at risk for Covid-19. They should be vaccinated as a priority[2].

Prenatal diagnosis is based on early combined screening (blood biochemical markers and early fetal ultrasound) and genetic analysis (karyotype or in situ hybridization) with evidence of an additional chromosome 21, usually complete,

[1] Press Release of the Academy's Rapid Communication Platform validated by the members of the Board of Directors on March 19, 2021.

sometimes present in only some cells (mosaic Trisomy). In rare cases, the third chromosome is partial (partial Trisomy 21). In prenatal care, the morphological ultrasound detects major malformations (heart disease, duodenal atresia, etc.) as well as minor signs. Medical follow-up is adapted to intellectual deficits and comorbidities. Scales of cognitive decline related to Alzheimer's disease have recently been adjusted for people with Down's syndrome[3].

In 2000, sequencing of chromosome 21 revealed the presence of more than 300 genes in three copies in Trisomy 21. The expression of many genes is not increased, by compensatory effects that remain to be elucidated[4]. Some genes, more involved than others in the appearance of the various symptoms, have been targeted in clinical trials with some success[5]. The disorders induced by Trisomy 21 evolve from birth to adulthood. They therefore require clinical evaluation throughout life. Age-specific therapeutic trials (new drugs or behavioral therapies) are needed. Without a precise classification model, taking into account age, comorbidities and the development of adapted measurement tools, the success of these trials remains compromised and the path towards personalized and precision medicine remains too narrow. Four windows of intervention are possible: prenatal, to act on early brain development; in children (from birth to adolescence), to compensate for cognitive disorders; in young adults (20 to 40 years), to detect and treat depressive syndromes and other comorbidities; and finally, after the age of 40, to prevent Alzheimer's disease disorders

The French National Academy of Medicine **stresses the importance of considering the disorders induced by Trisomy 21 throughout life, and recalls the need to:**

- ensure the effectiveness of prenatal screening for Trisomy 21 and birth defects throughout the country,

- facilitate the dissemination of measurement tools adapted to people with Down's syndrome, in particular cognitive scales for people aged over 35,

- improve the care of elderly people at risk of developing Alzheimer's disease,

- develop blood biomarkers of Alzheimer's disease progression,

- facilitate the integration of people with Down's syndrome into society, particularly into the world of work.

1. https://www.un.org/disabilities/documents/resolutions/a_res_66_149.pdf

2. Illouz T *et al*, Specific Susceptibility to COVID-19 in Adults with Down Syndrome. Neuromolecular Med.2021 Mar4:1-11. doi:10.1007/s12017-021-08651-5.

3. Benejam B *et al*, Diagnosis of prodromal and Alzheimer's disease dementia in adults with Down syndrome using neuropsychological tests. Alzheimers Dement (Amst). 2020 Jun 28; 12(1): e12047. doi:10.1002/dad2.12047.

4. Aït Yahya-Graison E, Aubert J, Dauphinot L, Rivals I, Prieur M, Golfier G, Rossier J, Personnaz L, Creau N, Bléhaut H, Robin S, Delabar JM, Potier MC. Classification of human chromosome 21 gene-expression variations in Down syndrome: impact on disease phenotypes. Am J Hum Genet. 2007 Sep;81(3):475-91. doi:10.1086/520000.

5. de la Torre R *et al*; TESDAD study group. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD):a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Neurol.2016 Jul;15(8):801-810. doi:10.1016/S1474-4422(16)30034-5