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Neurocognitive Degeneration in Down Syndrome: The Unsolved Mystery in Genetics

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Abstract

Down syndrome (DS) is a condition where a complete or segmental chromosome 21 trisomy causes variable intellectual disability, and progressive memory loss and neurodegeneration with age. It is the most commonly recognised cause of intellectual disability worldwide. All individuals with the condition have intellectual disability, typically associated with an IQ <70 and these deficits are related to structural and functional changes within the brain, some present from birth and others are acquired over time. The hippocampus, prefrontal cortex and cerebellum are particularly affected, and abnormalities in these regions are related to the cognitive deficits observed in individuals with Down syndrome, including impaired motor function, delayed speech and language, learning and memory problems, and behavioural and emotional turmoil. Many research groups have examined development of the brain in DS individuals, but studies on age-related changes that leads to cognitive deficit should also be considered, with the increased lifespan observed in DS. Here, we review literature on cognitive functioning, unique characteristics, Environmental considerations and recent findings on neurodegeneration in DS, as no specific treatment for DS has been discovered since our understanding of the mechanisms of the disorder is incomplete and this hampers the development of effective therapies regarding development of neuropathology and memory loss in DS.

Keywords: Down syndrome (DS); Intelligence quotient (IQ); Hippocampus; Prefrontal cortex; Cerebellum; Cognitive deficits; Neurodegeneration

Introduction

Down syndrome (DS, also known as Down's syndrome) or trisomy 21 is caused by the presence of three copies of chromosome 21 (Hsa21) instead of the usual two [1]. It is characterised by cognitive impairment [2] and the delayed and incomplete acquisition of motor skills [3] as a result of abnormal development of the nervous system [4]. Individuals with DS almost invariably develop Alzheimer's disease (AD) like symptoms (AD-DS). These include progressive dementia after 40 years of age, the onset of amyloid plaques, neurofibrillary tangles (NFTs) and neurodegeneration after 10-20 years [5,6] faster age-dependent motor decline that is an early marker for the onset of cognitive decline and health deterior-

ation [7,8] and a shorter mean life expectancy by approximately 28 years [9]. DS affects brain development, leading to lower brain weight with a small cerebellum, frontal cortex, and temporal cortex, as well as simplified appearances of sulci and a narrow superior temporal gyrus at autopsy [10,11]. Consistent with autopsy reports, high resolution MRI studies demonstrate lower overall brain volume, as well as a lower volume in the cerebellum, cingulate gyrus, frontal cortex, superior temporal cortex, and hippocampus, compared to the general population [12,13]. The triplicate copy of chromosome 21 leads to the overproduction of amyloid precursor protein [14], which is thought to contribute to early amyloid plaque accumulation (e.g., beginning in their teens and becoming nearly ubiquitous by 40 years of age; Mann 1988) that manifests with a striatum-dominant (i.e. Striatum-first) pattern. The distal part of the long arm of chromosome HSA21 is recognized as the "Down syndrome critical region and it is specifically associated

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with intellectual disability (ID) [15]. The phenotypic manifestation of DS has been identified and are discussed here.

Cognitive Functioning

Language

Despite considerable individual variability, individuals with Down syndrome have a characteristic profile of language and communication strengths and difficulties. Receptive language is typically stronger than expressive language, with phonology, syntax, and some aspects of pragmatics presenting particular developmental challenges [16]. A well-designed intervention studies are needed to determine the efficacy of commonly recommended approaches for developing language and literacy, with attention to outcomes in communication as well as academic and social domains.

Visuo-Spatial Ability

Visuo-spatial ability is the ability to process visual information that involves spatial relations, whereas verbal ability is the ability to process information that involves words and speech sounds. For example, young people with DS perform better on short term memory tasks when recalling visuo-spatial information such as sequences of block locations than when recalling verbal information such as sequences of digits or words [17-20]. Having a relative strength in visuo-spatial ability would be a clear advantage in certain aspects of life. It would make it easier to understand left from right, tie one's shoes, catch a ball, organize a desk or closet, or find one's way home from school or work. For those with DS, in many realms visual approaches may be more successful than verbal approaches. Indeed, visual approaches to reading and memory improvement have been promoted for this reason. In fact, visuo-spatial ability is commonly referred to as an area of strength in DS. In contrast to the commonly held view that nonverbal skills area strength in individuals with DS, are centre view by Yang and colleagues [2014] found that nonverbal, visuospatial processing shows an un even profile of skills, with some aspects of visuo-spatial abilities commensurate with general cognitive ability whereas, other aspects are below expected developmental level.

Environmental consideration

The epidemiological evidences in favour of the association between DS birth and environmental pollution are also surprisingly high, although controversial. Several pollution events are known to be followed by higher incidence of DS birth in an affected geographical locality. Early reports in the 1950s from USA suggested that fluoridation of water supplies might result in an increase in the frequency of DS birth. Subsequent comparison of overall DS birth rates in fluoridated and non-fluoridated areas in Massachusetts found no evidence for a difference. In this study prevalence rates of DS at birth were compared for Massachusetts residents ingesting fluoridated and non-fluoridated water. The observations included nearly all children born alive with DS in Massachusetts during the 17-year period 1950-1966. A rate of 1.5 cases per 1000

births was found both for fluoride-related births and appropriate comparison groups. Analysis of data from 51 American cities also found no difference in maternal age specific DS rates between fluoridated and non-fluoridated areas (Erickson, 1980).

Similarly, water contamination with pesticide trichlorfon has been reported to cause an outbreak of DS birth incidence. It was reported in the village of Hungary in 1990s to increase in teratogenic births, including that of DS. In Woburn, Massachusetts, toxic chemicals (industrial solvents, mainly trichloroethylene) from a waste disposal site were detected in municipal drinking water wells and people of this area reported increased incidence of several congenital anomalies followed up this finding by compiling an exposure score for residential zones in Woburn, using information on what fraction of the water supply in each zone had come from the contaminated wells annually since the start of the wells. The authors found a positive correlation between contaminated water use and higher birth-rate of DS in this locality. A second environmental factor that could affect the incidence of DS births is tobacco. Tobacco, a genotoxic agent, has been associated with a decrease in telomere length indicating a premature aging phenomenon. Ray et al., has recently found that mothers who used smokeless chewing tobacco had shorter telomere length and thus more susceptible to a meiotic non-disjunction error at gametogenesis.

Unique Characteristics of the Down Syndrome Population

Dementia

The most common cause of dementia is Alzheimer's disease (AD), with rates of prevalence increasing steadily from 60 years of age to reach almost 40% by the age of 85 [1]. AD is defined as the presence of neuritic plaques, which are composed of extracellular deposits of amyloid beta, and neurofibrillary tangles [2]. Individuals with DS are at an increased risk for developing early-onset Alzheimer disease(AD), as this is associated with several genetic factors that are over expressed on chromosome 21. Studies show that by the age of 40, almost 100% of people with Down syndrome who die have the changes in the brain associated with Alzheimer's disease. Amyloid precursor protein (APP), which is the abnormal breakdown that yields the toxic amyloid protein that forms plaques in the brain and probably damages brain cells and their connections, is coded for chromosome 21. Because people with Down syndrome have an extra copy of chromosome 21, they make 1.5 times as much APP as other people, and this seems to result in an excess tendency for the abnormal amyloid breakdown product to build up [21-26]. This appears to cause earlier appearance of the brain changes typical of Alzheimer's disease. However, a significant number of people with Down syndrome are older than 40 and show no signs of having Alzheimer's disease. It is not currently understood why changes to the brain that are typical of Alzheimer's disease do not necessarily produce the condition in people with Down syndrome.

Sensory Impairment

Hearing loss may be caused by a number of prenatal and postnatal conditions. These include a family history of childhood hearing impairment, anatomic malformations of the head or neck, low birth weight, severe perinatal asphyxia, perinatal infection (cytomegalovirus, rubella, herpes, syphilis, toxoplasmosis, bacterial meningitis), chronic ear infection, cerebral palsy, down syndrome, prolonged neonatal oxygen supplementation or administration of ototoxic drugs. In addition, high-risk neonates who survive formerly fatal prenatal or perinatal conditions may be susceptible to hearing loss from the disorder or its treatment. For example, sensorineural hearing loss may be a result of continuous humming noises or high noise levels associated with incubators, oxygen hoods, or intensive care units, especially when combined with the use of potentially ototoxic antibiotics.

Epilepsy

Epilepsy is a neurological condition that's caused by electrical disturbances in the brain that result in seizures, which can cause unusual behaviour, movements, or experiences, and sometimes a lack of awareness or loss of consciousness. Epilepsy is characterized by repeated and unpredictable interruptions of normal brain function called epileptic seizures. These seizures are caused by too much, abnormal, or synchronous communication between brain cells. Many people experience one seizure sometime in their life. In this condition, there's a surge of electrical energy that cause brain seizures, is believed to affect anywhere from 5 to 10 percent of children with DS. Historically, epilepsy has not been associated with Down syndrome.

Investigators such as Langdon Down and others in the 19th and early 20th century did not mention epilepsy at all, and until the late 1960ies epilepsy was considered rare in people with Down syndrome [13]. Today on the other hand, it is well known that epilepsy is more common in Down syndrome than in the general population [23,27]. The exact frequency of epilepsy in Down syndrome is difficult to determine, because each study uses different definitions for epilepsy and different inclusion criteria (such as institutionalized, or home reared, or both). More recent studies have reported a prevalence of seizures between 8% and 17 % [16,26] This prevalence range is higher than in the general population (1.5-5%), but lower than for individuals with other forms of cognitive disabilities (14-44%) [2,9].

Sleep Disorder

Many individuals with DS experience high rates of sleep problems, including obstructive sleep apnea, reduced rapid eye movement sleep (REM sleep or REMS; a unique phase of sleep in mammals, distinguishable by random/rapid movement of the eyes, accompanied with low muscle tone throughout the body, and the propensity of the sleeper to dream vividly), and poor sleep initiation and maintenance which leads to significant clinical consequences. These difficulties are associated with significantly poorer performance on tasks of attention, as well as memory storage/con-

solidation, and may exist in the context of co-morbid depression. Obstructive sleep apnea (OSA) is seen frequently in DS, and when present, it tends to be more severe. There is a 50-100% incidence of obstructive sleep apnea in individuals with Down Syndrome, with almost 60% of children with Down syndrome having abnormal sleep studies by age 3.5-4 years. The overall incidence of obstructive sleep apnea increases as children grow older. The prevalence of OSAHS in adults with Down syndrome is estimated at 35-42%. This is up to ten-times higher than in the general adult population. This increased prevalence is likely related to common anatomic abnormalities which include central apnea, low muscle tone in the mouth and upper airway, poor coordination of airway movements, narrowed air passages in the midface and throat, a relatively large tongue, and hypertrophy (enlargement) of adenoid and tonsillar tissues. Increased upper airway infections and nasal secretions and a higher incidence of obesity further contribute to collapse and obstruction of both the oropharynx and the hypopharynx when the individual is sleeping. Sleep disordered breathing has been shown to affect cognitive abilities, behaviours, growth rate and more the more serious consequences of pulmonary hypertension (abnormally high blood pressure in the arteries of the lungs) and cor-pulmonale (failure of the right side of the heart) [28-34]. Because of the high incidence of underlying congenital heart problems in individuals with Down syndrome, there is a higher risk of development of the more severe complications. Proper sleep hygiene and interventions are an essential component to optimizing cognitive functioning.

Conclusion

In conclusion, future holds potential hopes for DS patients and their mothers with simple measurements to decrease the risk and the effect of DS on family and community. The role of clinical geneticists is to encourage women in the childbearing period to take good nutrition, since infants and children with Down Syndrome can have feeding and drinking difficulties due to smaller oral cavity and low muscle tone in the facial muscles. Many children are mouth breathers due to smaller nasal passages, and may have difficulties coordinating sucking, swallowing and breathing whilst feeding. All of these factors can impact on how a child develops efficient oral and feeding skills which generally affects their nutrition which may probably leads to diet related issues like Thyroid Disorder, Diabetes, Constipation, Heart Defects, Structural Problems of the Gut, Food Intolerances and Allergies etc. In the same vein, the clinical geneticist should also provide DS mothers with help and support together with cognitive training and early intervention programs to their DS children.

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