Down syndrome (DS) is a genetic disorder that results from the presence of one extra chromosome 21 in the cell nucleus (trisomy 21), and is the most frequent cause of intellectual disability of genetic origin. Presently, Brazilian epidemiological data show that the incidence of live born infants with DS is 1:600, whereas in the USA this number is approximately 1:700. The large repertoire of phenotypic features and comorbidities generally listed in association with DS includes various congenital cardiac malformations, conductive and sensorineural hearing loss, increased risk of seizure disorder, atlantoaxial subluxation, and thyroid dysfunction (typically hypothyroidism; sometimes subsequent to transitory hyperthyroidism). Many features compatible with early aging are also common; including the universal presence of the characteristic Alzheimer-type pathology in the fourth decade of life and consequent increased frequency of dementia starting in the fifth decade. Besides these important DS components, the occurrence of alterations in visual and motor functions are also extremely frequent.

The visual system in persons with DS can be affected in several ways, including the increased incidence of refractive errors, accommodative imprecision, amblyopia, strabismus, spontaneous nystagmus, oculomotor and vestibular function abnormalities, decreased visual acuity, and reduced sensitivity for color and contrast. Studies in this field have yet to establish precisely whether the presentation of the ophthalmological abnormalities associated with DS is primarily of optical or neurological origin. However, studies conducted by John et al. (Mus musculus), using a combination of behavioral and objective assessments (visually evoked potential recordings), provided strong evidence of a neurosensory origin for visual acuity and contrast sensitivity deficits previously reported in infants and children with DS. Clinically, we observe that the use of refractive methods (glasses and contact lenses) only in rare instances fully correct visual acuity deficits in persons with DS.

Several forms of motor dysfunction are present universally in persons with DS. These are characterized by delays and alterations in motor development. Hypotonia, which is defined operationally as low resistance to passive movements, is observed also almost universally in children with DS, and so are articular hypermobility or hyperflexibility. From a functional point of view, however, these motor system disturbances are largely eclipsed by dysfunctions in dynamic motor capabilities, such as slow reaction time and alterations in postural reflexes and balance.

Traditionally, habilitative interventions, in the form of physical and occupational therapy services, have been applied to children with DS with the aim of maximizing motor development. Wide evidence exist in the literature supporting the efficacy of these strategies. Nevertheless, in general, such strategies are focused on the normalization of specific movements or groups of movements and do not differentiate between etiologies. Therefore, a child with DS tends to receive the same kind of intervention as a person without DS clinically displaying a similar delay in motor development. Thus, the choice of specific therapeutic approaches, as well as the optimization of a specific strategy for a particular case, is limited both by the lack of appropriate control studies and by the lack of a better understanding of the neural basis of the motor dysfunction that affects the individual with DS.

Similar to what happens in other fields of biomedical science, the use of animal models might be one of the ways to fill in the knowledge gaps in the areas related to both the visual deficits and motor dysfunction associated with DS. One of the obvious advantages in the use of animal models, especially the mouse (Mus musculus), is our ability to perform scientific studies that are technically or ethically not permissible in human beings. One mouse model in particular, the Ts65Dn, has been used preponderantly in the area of DS research. This mouse carries a trisomy for a large portion of the distal region of the long arm of mouse chromosome 21.
16 that has 60% of all human chromosome 21 homologous genes in this species.

Due to more or less obvious reasons, historically, most of the research involving murine models of DS have focused on the cognitive and neurological components of DS. In fact, such studies have generated more than 15 candidate pharmacological therapies targeted at improving the cognitive performance of persons with DS. Of these, one of the most advanced at present involves the drug memantine, which has produced a significant improvement in the ability of Ts65Dn mice to perform behavioral tasks designed to assess learning and memory16. These studies were reproduced independently in two different laboratories17,18. More importantly, these findings have been translated into the human domain through a pilot clinical trial19,20.

The findings of the research described above, as well as hundreds of other studies in mouse models of DS and other intellectual disabilities of genetic origin, provide us for the first time with a real chance to uncover the neural basis of various forms of visual deficits and motor dysfunction associated with DS. Obviously, it is important that we maintain a sober perspective, and that do not forget that mice are not miniature people. With this perspective in mind, we also should not overlook the fact that the torrent of new information, which we expect will be generated in the next few years, has a real potential to revolutionize the therapeutic outlook for DS. For example, given the possibility that a significant component of the visual deficit observed in persons with DS might be of neurological origin, we can envision a relatively near future in which the rational development of pharmacological therapies to improve visual and motor function of persons with DS may become possible. Under this scenario, the evolution of our understanding of the neural basis of visual and motor deficits specifically associated with DS may lead to the refinement and individualization of habilitative strategies for persons with DS.

Ongoing studies by our research team aim to enhance the information base on visual and motor functions, and to include the investigation of interactions between visual function, motor performance, and balance (similar to those published in this journal by Pinheiro eta20 and Rocha et al21 in the infant development follow-up and harmonization). We hope our research will help to revitalize the awareness of the importance of visual and motor functions (as well as the integration of these functions) for the quality of life of persons with DS. There is no doubt that cognition is key. However, in order to operate efficiently in society, we also require that sensory information reach our brains and that we possess an unimpaired ability to interact with the physical world through the motor system.

REFERENCES:


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