Characterization of genetic neurodevelopmental disorders at adult age, with a focus on 22q11.2 deletion syndrome

Impact

The overall aim of this thesis was to gain insight into conditions that develop, or are present, in adults with a genetic syndrome, with a focus on 22q11.2 deletion syndrome (22q11.2DS). Study topics included parkinsonism, otolaryngology, ophthalmology and post-traumatic stress. In this chapter the societal and research impact of the studies included in this thesis are discussed.

The main findings included an increased risk of Parkinson's disease, hearing loss, chronic middle ear infections, swallowing difficulties, balance problems, obstructive sleep apnea (a sleep disorder), refractive errors (for example farsightedness) and post-traumatic stress in adults with 22q11.2DS. Treatment options exist for most of these conditions and preferably start as soon as possible in order to minimize disease burden and improve quality of life. The studies described in this thesis include recommendations for clinical care, mostly aimed at improving screening in order to early detect conditions that may frequently be present in adults with 22q11.2DS. A summary of the most important recommendations is provided in the first section of the discussion in **chapter 8**. Some of the published findings and recommendations have already been incorporated in the recently updated international clinical practice recommendations for children and adults with 22q11.2DS,[1, 2] that provide guidance for clinicians treating individuals with 22q11.2DS and for genetic counseling. Results are relevant to clinicians and other care givers of various medical specialties. Therefore, results have been presented at local, national and international symposia and conferences for patient organizations and for clinicians that treat individuals with 22q11.2DS including clinical geneticists, physicians for people with an intellectual disability, neurologists, otolaryngologists and ophthalmologists. In addition to scientific publications in peer-reviewed journals, results related to sensory deficits and post-traumatic stress in adults with 22q11.2DS have been made available in Dutch in a magazine for clinicians who treat people with an intellectual disability.

For genetic syndromes that were associated with parkinsonism described in **chapter 2**, recommendations were provided to improve recognition

and treatment of parkinsonism, Parkinson's disease in particular, in these genetic syndromes. This study indicated that regular antiparkinsonian medication showed positive effects in most individuals with (suspicion of) Parkinson's disease, which is of direct clinical relevance. In this study it is recommended that dopaminergic imaging techniques may be considered in patients with a genetic syndrome - who often use anti-psychotic medication - to distinguish neurodegenerative parkinsonism (e.g., Parkinson's disease) from parkinsonism as side-effect of medication. In addition to a scientific publication, results have been presented at international and national conferences for movement disorders specialists and other neurologists, as well as for physicians for people with intellectual disabilities.

The goal of sharing results with different target audiences was to make clinicians aware of the conditions that were frequently present in adults with 22q11.2DS or other genetic syndromes, to improve screening and to emphasize the possibilities for treatment that may ultimately result in better care for adults with a genetic syndrome. In addition, results of the studies included in this thesis demonstrated how a genetic diagnosis may improve clinical care for individuals with an intellectual disability, since some conditions were more frequently seen in adults with 22q11.2DS compared to other genetic syndromes or adults with an intellectual disability in general. For example, knowledge of an increased risk of early-onset Parkinson's disease in 22q11.2DS compared to the general population and people with an intellectual disability, contributes to recommendations for screening specifically for adults with 22q11.2DS. Therefore, a genetic diagnosis may facilitate a more personalized approach by care providers.

Findings of these studies provide information to adults with 22q11.2DS and their relatives about what may be expected at adult age. In addition, it may raise awareness of an increased risk of conditions such as Parkinson's disease or hearing loss at relatively young-adult age and may help adults with 22q11.2DS or relatives to seek help at an early stage. To make results directly available to adults with 22q11.2DS and their relatives, a presentation was given about post-traumatic stress in 22q11.2DS at the information day of the Dutch 22q11 family organization Stichting Steun 22Q11, and results have been shared via their annual magazine, 's Heeren Loo website, and

via newsletters to adults with 22q11.2DS who participated in studies at Maastricht University Medical Center, which together with 's Heeren Loo, offers a specialized clinic for adults with 22q11.2DS.

Results of the studies included in this thesis may inform future studies aimed at finding or improving treatment for conditions that are frequently present in adults with 22q11.2DS. For example, a study of the efficacy of treatment for trauma in adults with 22q11.2DS has recently started.

In addition to the societal impact of the included studies, mostly health care related, results may also have research implications.

The studies described in this thesis that were performed in adults with 22q11.2DS may suggest that 22q11.2DS is associated with precocious aging, which has also been suggested in some other genetic syndromes such as Down syndrome. Because previous research already provided substantial knowledge of genes and affected mechanisms involved in the development of genetic syndromes such as 22q11.2DS, they may serve as a model to study mechanisms and novel treatment options of age-related conditions such as Parkinson's disease. Recognition of conditions that are common at adult age in genetic syndromes enables future studies that use mouse models or (stem)cells of genetic syndromes. Results of these studies may not only be relevant to adults with a genetic syndrome but may also improve our understanding of the etiology and treatment of these age-related conditions in the general population.

References

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