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

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Summary

The overall aim of this thesis was to characterize genetic neurodevelopmental disorders (GNDs) at adult age, with a focus on 22q11.2 deletion syndrome (22q11.2DS). Study topics included parkinsonism, otolaryngology, ophthalmology and trauma-related disorders. In this appendix, a summary of the individual studies is presented. **Chapter 1** provides a general introduction to 22q11.2DS and study topics included in this thesis.

In **chapter 2** results are discussed of a systematic review of the literature on parkinsonism in GNDs. It is increasingly recognized that individuals with GNDs can suffer from parkinsonism, including neurodegenerative parkinsonism. With advances in clinical genetic testing for neurologic disease, the number of GNDs associated with parkinsonism is growing fast. In this chapter an overview of the literature is provided that reports on parkinsonism in GNDs. The literature search yielded over two hundred full-text publications for data-extraction, reporting on 422 individuals with 69 different GNDs and parkinsonism. The five most reported GNDs from most to least frequent were: beta-propeller protein-associated neurodegeneration, 22q11.2DS, Down syndrome, cerebrotendinous xanthomatosis, and Rett syndrome. Notable findings were an almost equal male to female ratio, an early median age of motor onset (26 years old), and rigidity being more common than rest tremor. Results of dopaminergic imaging and response to antiparkinsonian medication often supported the neurodegenerative nature of parkinsonism. Moreover, neuropathology results showed neuronal loss in the majority of cases. Proposed disease mechanisms included aberrant mitochondrial function and disruptions in neurotransmitter metabolism, endosomal trafficking, and the autophagic-lysosomal and ubiquitin-proteasome system. Together, many GNDs have been associated with parkinsonism and results were often supportive of neurodegenerative parkinsonism, with typical findings with dopaminergic imaging and a good response to antiparkinsonian medication. Clinicians who take care of individuals with GNDs included in this study should be aware of a possible increased risk of parkinsonism, that may have an atypical presentation. Similarly, parkinsonism combined with a history of a neurodevelopmental disorder could prompt clinicians to consider

genetic testing. Further recognition of parkinsonism in these GNDs may provide insights into the mechanisms causing parkinsonism in the general population, crucial for the development of disease-modifying treatments.

In **chapter 3** the estimated prevalence of Parkinson's disease is examined in adults with 22q11.2DS. An increased risk of Parkinson's disease, of 20-to-70-fold, has previously been suggested in adults with 22q11.2DS. However, prevalence estimates were based on only 68 individuals with 22q11.2DS, at a relatively young age of 35 to 64 years. A multicenter cross-sectional study was conducted that included 856 adults (47% male, at mean age 46.5 ± 15.4 years) with 22q11.2DS who visited one of the specialized 22q11.2DS clinics in the Netherlands (Maastricht University Medical Centre and 's Heeren Loo), Belgium (University Hospital Leuven), Canada (Dalglish Family 22q Clinic, Toronto) and Chile (University of Santiago). Parkinson's disease was defined as a clinical diagnosis by a neurologist, and presence of bradykinesia and at least one of either rest tremor or rigidity. Suspected Parkinson's disease was defined as a clinical diagnosis of Parkinson's disease or a clinical suspicion of Parkinson's disease without complying to the formal criteria. The results indicate a prevalence of 1.8% for Parkinson's disease (95% CI: 0.9 – 2.6) and 3.4% (95% CI: 2.2 – 4.6%) in case adults suspected of Parkinson's disease were included. A sharp increase in the prevalence of Parkinson's disease was seen in adults with 22q11.2DS aged 50 years and older (11.7%). In contrast to Parkinson's disease in the general population, male sex was not associated with an increased risk in adults with 22q11.2DS. Based on these findings, periodic evaluation of motor symptoms by a neurologist, preferably a movement disorder specialist, seems justified in adults with 22q11.2DS aged 40 years and older. Individuals with 22q11.2DS at any age showing parkinsonian motor signs may benefit from careful monitoring and referral for neurological examination in case of doubt of the etiology.

In **chapter 4** results regarding hearing loss and otolaryngological conditions in adults with 22q11.2DS are reported. Previous studies showed an increased prevalence of hearing loss and chronic otitis media in 22q11.2DS. Since most studies focused on children, and the knowledge on adults is still scarce, the aim of this study was to report on hearing and otolaryngological findings in adults. Therefore, a cross-sectional study was

conducted including 60 adults (42% male, median age 25.0 (range 16-74) years) with 22q11.2DS who visited an otolaryngologist and audiologist at the 22q11.2 expert center in Maastricht. Results of this study indicate a high prevalence, of 78.3%, of hearing loss in adults with 22q11.2DS, which was mostly high-frequency sensorineural loss. Higher age and a history of chronic otitis media were associated with more severe hearing loss. Otolaryngologic conditions with possible treatment implications included chronic otitis media (56.7%), globus pharyngeus (18.3%), balance problems (16.7%) and obstructive sleep apnea (8.3%). Based on these findings, periodic audiometric screening is recommended in all adults, including high-frequency ranges, and otolaryngological examination at least once.

In **chapter 5** results are presented of a systematic literature review and multi-center cross-sectional study of ocular findings in children and adults with 22q11.2DS. The systematic literature search yielded four articles, describing 270 individuals and the cross-sectional study included 132 individuals (45% male, median age 8.9 (range 0-56) years). Most reported ocular findings were retinal vascular tortuosity (32-78%), posterior embryotoxon (22-50%), eye lid hooding (20-67%), strabismus (12-36%), amblyopia (2-11%), ptosis (4-6%) and refractive errors, of which hyperopia (6-48%) and astigmatism (3-23%) were most common. Visual acuity was (near) normal in most individuals (91-94%).

Results of this study indicate that clinicians should be aware of refractive errors, strabismus and amblyopia, and the beneficial result of detection and correction at an early age. Therefore, standardized ophthalmic and orthoptic screening is recommended in children with 22q11.2DS at the age of three years or at diagnosis, and a low-threshold for referral in adults.

In **chapter 6** differences are explored in retinoneural and retinovascular parameters between adults with 22q11.2DS and controls, and in relation to age. Because retinal and cerebral tissue share embryological, physiological and anatomical characteristics, retinal blood vessel morphology and retinal nerve fiber layer (RNFL) thickness have been proposed as non-invasive biomarkers for psychiatric and neurodegenerative disorders. Central retinal artery and vein equivalent, fractal dimension, and vascular tortuosity,

obtained through fundoscopy, and peripapillary RNFL and macular thickness, obtained through optical coherence tomography, were compared between adults with 22q11.2DS and sex- and age-matched controls. Results indicate that retinal vascular fractal dimension and tortuosity are significantly higher in adults with 22q11.2DS compared to controls. In addition, significant negative correlations with age were found for fractal dimension and RNFL thickness in the global, temporal inferior and temporal superior segments in adults with 22q11.2DS, but not in controls. These findings support future studies that focus on retinal fractal dimension and RNFL thickness as potential biomarkers for age-related manifestations in 22q11.2 including psychotic and (early) neurodegenerative disorders.

In **chapter 7** findings are presented related to trauma and post-traumatic stress disorder (PTSD) in adults with 22q11.2DS. Previous studies indicated a lower prevalence of PTSD in individuals with 22q11.2DS compared to the general population; 0.9% *vs* 3.6% respectively. The prevalence of PTSD was hypothesized to be higher. Therefore, PTSD prevalence, and potential predictors to PTSD, were studied in 112 adults with 22q11.2DS (45% male, mean age 32.5 ± 12.4 years). A chart review was performed of individuals with 22q11.2DS who visited the Dutch specialty clinic for adults with 22q11.2DS at Maastricht or 's Heeren Loo. Results indicate a prevalence of PTSD of 8.0% (95% CI 3.0% - 13.0%) in adults with 22q11.2DS. A traumatic event was experienced in 23 adults (20.5%): mostly sexual violence (10.7%) or serious injury (9.8%). An additional 17 adults (15.2%) experienced other potential traumatic events, including bullying (11.6%) and multiple hospitalizations/surgeries (3.6%). Treatment for trauma was reported in 20 adults (17.9%), of whom 8 with PTSD, and included Eye Movement Desensitization Reprocessing (EMDR, 17.0%) and cognitive behavioral therapy (1.8%). Neither sex nor full-scale intelligence quotient was associated with PTSD. Findings of this study indicate that PTSD and trauma appear to be prevalent in adults with 22q11.2DS, and may have been overshadowed by, or attributed to, other psychiatric disorders in previous research. Previous studies have shown that treatment strategies for trauma, including EMDR, were effective in people with an intellectual disability in general. Given the large impact PTSD can have on a person's wellbeing, clinicians should be alert to PTSD in 22q11.2DS in order to minimize

psychiatric burden. Systematic studies in individuals with 22q11.2DS are needed to improve diagnosis, using strategies adjusted to their cognitive profile and including attention for seemingly innocuous life events that may be traumatic, and to evaluate the efficacy of treatments in this population.

In **chapter 8** results of individual studies of this thesis are discussed in a broader context and in relation to previous research. Collectively, studies included in this thesis seem to point to precocious aging in adults with 22q11.2DS. In addition, this chapter provides recommendations for future research, including longitudinal studies over the life course of individuals with 22q11.2DS or other GNDs and cross-GND studies that may aid in our understanding of the (shared) underlying mechanisms and move treatment discoveries.

In **chapter 9** the impact of the included studies in this thesis is discussed on society, including health care, and science. Mostly, impact was achieved by implementation of study results and recommendations described in this thesis into the clinical recommendations for children and adults with 22q11.2DS, and by sharing results with a broad audience of physicians of various medical specialties and adults with 22q11.2DS and their families in order to improve care and quality of life of adults with 22q11.2DS.