e-Methods

Literature review

To further characterize Parkinson's disease (PD) in 22q11.2 deletion syndrome (22q11.2DS), we attempted to identify all individuals with coexistent 22q11.2DS and PD (living or deceased) published in the literature (table e-1). First, we searched publications with the search engines PubMed and Web of Science using the terms "(22q11.2 OR velocardiofacial OR DiGeorge) AND (Parkinson's disease OR parkinsonism OR bradykinesia OR tremor OR rigidity)" on November 1, 2016. Potentially relevant articles and conference abstracts were accessed in order to review the full text, after excluding duplicate publications. We excluded publications that did not report original data on individuals with coexistent 22q11.2DS and PD. Second, we searched through a personal library of publications (E.B.) related to 22q11.2DS using the term "parkinson" to capture any potential 'hidden cases' (patients with 22q11.2DS reported in the literature with respect to another disease, with PD comorbidity) that were not found with the abovementioned search strategy or through examined associated reference lists. Third, we added publications identified through personal communications, including two articles published during preparation of this manuscript.[1,2]

Thirty-five cases (28 male, 80.0%; 34 clinically confirmed, 94.1%) were identified.[1-23] One patient (a 30-year-old man at last follow-up) with progressive tremors, bradykinesia, rigidity, and gait changes, on three antiparkinsonian drugs [response to levodopa treatment was not reported], was classified as having *suspected* PD in the present study, since the authors indicated that they could not confirm a PD diagnosis due to "possible clozapine-induced parkinsonism".[13]

Other means of case identification

In order to supplement cases identified from the existing literature we employed several other case finding strategies. Members of the International Parkinson and Movement Disorder Society (MDS) were notified about this study and instructed to contact us to contribute any potential cases through a posting that appeared on the notices page of the MDS website (http://www.movementdisorders.org) from November 25 to December 16, 2016. All members of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome (22q11.2DS IBBC) and the Dutch society of physicians specialized in intellectual disability medicine (NVAVG) were informed about the study through an email blast and asked to contribute candidate cases in October 2016. We screened a large locally available 22q11.2DS cohort primarily ascertained through adult congenital cardiac, psychiatric, and genetic services using active screening and/or clinical referrals (living, n = 260 [122 male], aged 17.2-66.2 years, median age = 27.7 years) for PD diagnoses before November 25, 2016.[10,24] We also searched the database of death record information of this Canadian cohort (n = 24 [11 male]) to identify deceased cases. Finally, we contacted international clinicians who had approached us by email and in-person at conferences previously following our initial publication on 22q11.2DS-associated PD with additional possible cases with coexistent 22q11.2DS and PD.[7]

Ten additional 22q11.2DS-associated PD cases (4 male; 9 confirmed) were identified. PD diagnosis could not be clinically confirmed in a 48-year old female with progressive parkinsonism, where the differential diagnosis included antipsychotic-induced parkinsonism, and parkinsonism of unknown etiology. This patient was recently assessed by an experienced movement disorders neurologist (A.E.L.), was prescribed a trial treatment with a low dose of levodopa (after a failed trial with amantadine) with mild improvement, and was classified as having *suspected* PD.

Characterization of cases

E-mail invitations to provide detailed clinical data on identified cases were sent to the senior authors of the identified publications reporting on one or more case(s) with 22q11.2DS and PD, and to physicians known to be aware of one or more additional case(s) identified through one of the other

case finding strategies. A maximum of 5 reminders were sent. All participating physicians were provided with a cover letter outlining the aims and methods of the study and were asked to complete two anonymized checklists for collection of relevant clinical data (table e-2). Briefly, data collected included information on demographic variables (sex, ethnicity, age at most recent assessment, and age at death), medication use, genetics (referring to 22q11.2DS status as well as PD risk genes), family history of movement disorder(s), clinical features of 22q11.2DS, and PD expression based on clinical assessment, lifetime medical chart reviews, and neuroimaging data. Respondents were asked for additional information and/or clarification through e-mails in the event of missing data, unclear answers, and/or conflicting information. In cases of doubt, we used the best estimate for age data. In the case that age at motor symptom onset was reported as 'before age X', the estimated age at onset for that person was considered age X minus one year. In the event that age at 22q11.2DS diagnosis was reported as 'after death/last assessment' (applicable in 2 cases), the age at 22q11.2DS diagnosis was considered age at death/last assessment plus one year. If data was missing it was characterized as 'unknown'. Follow-up time was defined as age at last assessment or death minus age at motor symptom onset. Psychiatric symptoms with onset around (≤1 year before), or after, the PD diagnosis were characterized as 'new' symptoms. We systematically compiled and coded the data obtained from all previously published and new, cases. We used a standard EOPD definition of age at onset <45 years.[25]

Inclusion and exclusion criteria for cases identified in the study

We included only those individuals with 22q11.2DS with a molecularly confirmed 22q11.2 deletion in the commonly deleted 22q11.2 region.[26] Clinical genetic testing was by fluorescence in situ hybridization (FISH) using a targeted probe (n = 29, 64.4%), genome-wide microarray (n = 18, 40.0%), or multiplex ligation-dependent probe amplification (MLPA) (n = 2, 4.4%). In five patients, 2 genetic tests were used. In one case we were only able to retrieve information that "the 22q11.2 deletion was genetically proven". We defined PD as present when a neurologist had made a clinical diagnosis of PD in the presence of bradykinesia and at least one of either rest tremor or rigidity.[25] In one patient with bradykinesia, rigidity, resting tremor, and gait changes, and a positive history of one first-degree and three second-degree relatives for PD, we considered the diagnosis confirmed based on the typical pattern of severely reduced dopamine transporter (DAT) binding on DAT imaging,[5] despite the fact that, a few years prior to the DAT scan, at the last assessment by the neurologist the PD diagnosis was deferred due to antipsychotic use (olanzapine) at the time of assessment. We thus included all cases with coexistent 22q11.2DS and confirmed (n = 43) or suspected PD (n = 2). Individuals with 22q11.2DS and drug-induced parkinsonism, or parkinsonism of unknown etiology were excluded.[6] For example, we excluded a 46-year old woman with symmetric tremors, bradykinesia, rigidity, postural instability, and swallowing disturbances that had worsened from baseline, because of antipsychotic use (zuclopenthixol 10 mg/day) and bilateral symmetric increased binding of the DAT ligand 18F-PRO4.MZ in the putamen and caudate nuclei (125-130% of control) with dopaminergic imaging.[1]

Figure 1 summarizes the case ascertainment strategy for the 45 individuals with 22q11.2DS-associated PD (n = 43, 95.6%, clinically confirmed) identified. Ethnicity for the 45 cases with sufficient data was: 36 (80.0%) Caucasian, 3 (6.7%) Asian, and 6 (13.3%) unknown. Detailed data were available for 36 (80.0%) cases, including 26 (74.3%) of the 35 previously reported cases. In the majority of cases (29/43, 67.4%), the neurologist confirming the PD diagnosis was a specialist in movement disorders; for the remaining cases the neurologist was not a subspecialist (n = 6, 14.0%) or subspecialty was unknown (n = 8, 18.6%).

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