Movement Disorder Phenotypes in Children With 22q11.2 Deletion Syndrome

The 22q11.2 deletion syndrome (22q11.2DS) is associated with a broad spectrum of clinical phenotypes, including congenital heart defects and immune deficiencies. In addition, there is also an increased risk of psychiatric disorders, cognitive deficits, and functional motor impairments.[1-3] To date, a systematic examination of movement disorders has not been undertaken in this group.

Nineteen participants with 22q11.2DS (11 male: 8 female; median age, 12.7 years; range, 6.8–17.1 years), and 13 sibling controls (7 male: 6 female; median age, 11.2 years; range, 7.5–17.5 years) were recruited following informed consent, via ongoing cohort studies at Cardiff University (CU) with no further selection criteria applied. Ethical approval was provided by CU School of Medicine Research Ethics (reference: 17/69). The presence of the 3-Mb 22q11.2 deletion was confirmed using the Infinium PsychArray-v1.1 (Illumina) platform, fluorescence in situ hybridization or genetic arrays through the National Health Service medical genetics departments.

Data collected included sex, age at examination, medical comorbidities, and developmental history alongside assessment of full-scale intelligence quotient (IQ), psychiatric symptoms, and coordination performance. Motor assessment involved a standardized videotaped clinical examination using a modified Burke-Fahn-Marsden Dystonia (BFMDRS) rating scale protocol.[4] Examinations were reviewed independently by 3 neurologists blinded to all clinical information. Reviewers indicated if a movement disorder was observed and determined its phenomenology and body distribution. A movement disorder was considered present when there was agreement between all neurologists. Statistical analysis was carried out in R, using Fisher's exact tests, chi-squared tests, Pearson's correlations, and *t* tests as appropriate.

Sample demographics are presented in Table 1. There was a higher rate of movement disorders in the 22q11.2DS group compared with controls (P = 0.0002), with consensus agreement for a movement disorder in 18 of 19 children with 22q11.2DS (94.7%) compared with 4 of 13 of controls (30.8%). Dystonia was the most common movement disorder subtype, in isolation (94.4%, n = 17) and combined with upper limb distal jerks (5.6%, n = 1). The limbs and craniocervical region were most commonly affected, with upper limb involvement in all 18 cases (Videos 1–3). Three of 4 controls displayed isolated dystonia, with upper limb involvement in all 4. In the 22q11.2DS cohort, dystonia severity was mild (mean BFMDRS, 24.93/120) but was associated with lower IQ (r = −0.52, P = 0.03) and higher anxiety symptoms (r = 0.57, P = 0.03).

This is the first cohort study investigating the prevalence and type of movement disorders in young people with 22q11.2DS. Dystonia was the most commonly observed subtype, although these features were mild and tended to be associated with action. Identification of true movement disorders is often challenging in this age range, but the frequency of dystonic signs in the 22q11.2DS group indicate that they were associated with the 22q11.2DS phenotype, rather than neuromotor immaturity. More severe dystonia was associated with lower IQ and higher levels of anxiety. The 22q11.2 deletion is known to affect brain development,[5,6] and genes in the region such as *COMT* are expressed in the brain.[7] Our study is a cross-sectional, longitudinal examination throughout childhood, adolescence, and into adult-life and is required to gain a more comprehensive understanding of the 22q11.2DS motor phenotype. Although this cohort is relatively small, the high rate and preponderance of dystonia indicate that it is likely part of the neurodevelopmental phenotype of 22q11.2DS.

Author Contributions

Adam C Cunningham had a major role in the acquisition of data; interpreted the data; and drafted the article for intellectual content. Wilson Fung had a major role in the acquisition of data and revised the article for intellectual content. Thomas H. Massey had a major role in the acquisition of data and revised the article for intellectual content. Jeremy Hall interpreted the data and revised the article for intellectual content. Michael J. Owen interpreted the data and revised the article for intellectual content. Marianne B. M. van den Bree designed and conceptualized the study, interpreted the data, and revised the article for intellectual content. Kathryn J. Peall designed

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TABLE 1. Cohort demographic, motor, and nonmotor characteristics

	22q11.2DS n (%)/mean (SD)	Sibling controls n (%)/mean (SD)	22q11.2DS versus sibling controls *P* (95% CI)	22q11.2DS cohort: correlation analysis with BFMDRS severity Scores Correlation coefficient, *r* (*P*)
Total cohort (M : F)	19 (11:8)	13 (7:6)	—	
Age at examination (years), Median (range)	12.70 (6.8–17.1)	11.12 (7.5–17.5)	0.79 (−2.8 to 2.2)	−0.24 (0.34)
FSIQ	78.83 (10.06)	109 (15.13)	**<0.0001 (21.16–39.64)**	**−0.52 (0.03)**
BFMDRS severity score (maximum possible score, 120)	24.93 (8.17)			
Medication				
≥1 Medication prescribed	12 (63.2%)	0 (0%)	**0.0004**[b]	
Melatonin	5 (26.3%)	—	—	
Antibiotics	4 (21.1%)	—	—	
Laxatives	3 (15.8%)	—	—	
Vitamin/mineral supplementation	3 (15.8%)	—	—	
Antidepressants	1 (5.3%)	—	—	
Medical comorbidities				
Cardiac defect	13 (68.4%)	0 (0%)	**0.0001**	
ASD/VSD	5 (26.3%)	—	—	
Tetralogy of Fallot	4 (21.1%)	—	—	
Other	4 (21.1%)	—	—	
Past/present seizures	1 (5.3%)	0 (0%)	>0.99	
Cleft lip/palate	6 (31.6%)	0 (0%)	0.06	
Recurrent respiratory infections	7 (36.8%)	0 (0%)	**0.02**	
Recurrent ear infections	6 (31.6%)	1 (7.7%)	0.20	
Psychiatric symptoms				
ADHD	7 (36.8%)	1 (7.7%)	0.10	
Anxiety disorder (overall)	5 (26.3%)	1 (7.7%)	0.36	
Social phobia	3 (15.8%)	0 (0%)	0.25	
Generalized anxiety disorder	1 (5.3%)	0 (0%)	>0.99	
Specific phobia	1 (5.3%)	1 (7.7%)	>0.99	
ADHD count score	3.39 (3.38)	1.00 (3.16)	0.07 (−2,39 to 1.3)	0.41 (0.10)
Anxiety count score	2.13 (3.18)	1.75 (2.96)	0.78 (−3.17 to 2.42)	**0.57 (0.03)**
Autism trait symptoms score	11.43 (5.16)	2.50 (2.27)	**<0.0001 (−12.55 to −5.30)**	0.42 (0.16)
Developmental history				
Preterm birth	4 (21.1%)	5 (38.5%)	0.43	
Failure to thrive	8 (42.1%)	0 (0%)	**0.01**	
Feeding difficulties	16 (84.2%)	1 (7.7%)	**<0.0001**	
Parental reported clumsiness	15 (78.9%)	3 (23.1%)	**0.003**	
Talking by 2 years of age	6 (31.6%)	12 (92.3%)	**0.0009**	
Walking by 1.5 years of age	11 (57.9%)	11 (84.6%)	0.14	
Statement of educational needs/education and health care plan	13 (68.4%)	1 (7.7%)	**0.0009**	
Age at riding a bike (years), median (range)	6.5 (5–10)	5 (3.5–7)	0.09 (−27.6 to 2.1)	0.02 (0.95)
Age at being able to button (years), median (range)	6.2 (3.5–10.25)	4 (3–6.5)	**0.008 (−41.6 to −7.0)**	−0.10 (0.79)
Age at being able to do laces (years), median (range))	9.75 (6–11)	6.9 (5–8.7)	**0.008 (−47.3 to 8.4)**	0.20 (0.63)
Movement disorder				
Evidence of movement disorder on examination	18 (94.7%)	4 (30.8%)	**0.0002**	
Dystonia	17 (94.4%)	3 (23.1%)	**0.0002**	
Distal UL jerks (possible myoclonus/ possible chorea)	1 (5.6%)	1 (7.7%)	>0.99	
Body part affected				
Eyes	0 (0%)	0 (0%)	>0.99[b]	
Oromandibular rgion	6 (31.6%)	0 (0%)	**0.0** [b]	
Cervical	8 (42.1%)	1 (7.7%)	**0.05**	
Upper limbs	18 (94.7%)	4 (30.8%)	**0.0002**	
Trunk	0 (0%)	0 (0%)	>0.99	
Lower limbs	8 (42.1%)	3 (23.1%)	0.45	

(Continues)

TABLE 1. Continued

	22q11.2DS n (%)/mean (SD)	Sibling controls n (%)/mean (SD)	22q11.2DS versus sibling controls *P* (95% CI)	22q11.2DS cohort: correlation analysis with BFMDRS severity Scores Correlation coefficient, *r* (*P*)
DCDQ scores				
Overall	37.37 (12.54)	69.75 (6.90)	**<0.0001 (24.27–40.49)**	−0.29 (0.24)
Control during movement	15.21 (5.35)	28.17 (2.89)	**<0.0001 (9.51–16.4)**	−0.11 (0.65)
Fine motor score	10.95 (3.63)	19.33 (1.44)	**<0.0001 (6.13–10.64)**	−0.41 (0.09)
General coordination score	11.21 (5.34)	22.25 (3.98)	**<0.0001 (7.4–14.7)**	−0.29 (0.23)

ADHD, attention deficit hyperactivity disorder; DCDQ, Developmental Coordination Disorder Questionnaire; FSIQ, full-scale intelligence quotient; SCQ, Social Communication Questionnaire; UL, upper limbs; Control during movement, fine motor score, and general coordination score all form subsections of the DCDQ. The SCQ is used to measure Autism Trait Symptom Score, ADHD, and anxiety symptoms were measured using the Child and Adolescent Psychiatric Assessment (CAPA).
Bold denotes $P \leq 0.05$.

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Search terms: [161] All Movement Disorders, [162] Dystonia, [228] Developmental Disorders, [230] Child Psychiatry, [91] All Genetics.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.