Movement Disorders and Other Motor Abnormalities in Adults With 22q11.2 Deletion Syndrome

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Abstract

Movement abnormalities are frequently reported in children with 22q11.2 deletion syndrome (22q11.2DS), but knowledge in this area is scarce in the increasing adult population. We report on five individuals illustrative of movement disorders and other motor abnormalities in adults with 22q11.2DS. In addition to an increased susceptibility to neuropsychiatric disorders, seizures, and early-onset Parkinson disease, the underlying brain dysfunction associated with 22q11.2DS may give rise to an increased vulnerability to multiple movement abnormalities, including those influenced by medications. Movement abnormalities may also be secondary to treatable endocrine diseases and congenital musculoskeletal abnormalities. We propose that movement abnormalities may be common in adults with 22q11.2DS and discuss the implications and challenges important to clinical practice.

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Keywords

22q11 deletion syndrome; movement disorders; adult; parkinsonian disorders; myoclonus; essential tremor; antipsychotic agents

INTRODUCTION

The phenotypic expression of 22q11.2 deletion syndrome (22q11.2DS) is highly variable and clinical features differ depending on the age of the patient [Bassett et al., 2011]. In addition to its classic physical manifestations such as congenital heart defects, palatal abnormalities and hypocalcemia, diverse neuropsychiatric manifestations beyond the associated learning disabilities are common. For example, autism spectrum, attention deficit hyperactivity, anxiety, and schizophrenia spectrum disorders are highly prevalent [Schneider et al., 2014]. An increasing number of reports suggest that 22q11.2DS may be accompanied by a significant cognitive and functional decline across the lifespan [Duijff et al., 2012; Evers et al., 2014; Schneider et al., 2014].

Movement abnormalities are common in children and adolescents with 22q11.2DS. These include hypotonia in infancy, delayed gross-motor milestones [Swillen et al., 1999], specific motor deficits in axial stability [Roizen et al., 2010], deficits in psychomotor speed [Howley et al., 2012], problems with coordination and balance [van Aken et al., 2009], asymmetric crying face [Pasick et al., 2013], seizures, and tremor or tetany as a result of hypocalcemia [Weinzimer, 2001].

Later-onset movement disorders and other motor abnormalities (movement abnormalities) may also be found in adults with 22q11.2DS. Notably, an increased risk of early-onset Parkinson disease has been reported [Butcher et al., 2013]. However, brain dysfunction may lead to various clinical manifestations including neuropsychiatric manifestations and movement abnormalities [Moreno-De-Luca et al., 2013]. An analogy may be found in the neurologic disorders associated over life with trisomy 21, where infantile spasms are common in infancy and Alzheimer dementia arises in later years [Lott and Dierssen, 2010]. Moreover, a wide range of co-morbid features (e.g., congenital abnormalities, psychotropic, and antiepileptic medication) may be associated with movement abnormalities in adults with 22q11.2DS. Given that adults with 22q11.2DS represent an increasing population related to improved childhood survival, advances in pediatric care, and improved availability of genetic testing [Carotti et al., 2008; Costain et al., 2011], knowledge about movement abnormalities beyond childhood is important to inform best-practices for diagnoses and treatment.

We report on five adults with molecularly confirmed 22q11.2DS, illustrative of the complex, multiple, and often interacting factors associated with 22q11.2DS that may lead to movement abnormalities in the adult population. We highlight the key clinical findings relevant to the primary movement abnormalities. Additional secondary or minor movement abnormalities are provided in Table I. We propose that movement abnormalities are common in adults with 22q11.2DS and discuss the implications and associated challenges for clinical practice.

CLINICAL REPORTS

Patient 1: Gait Disorder—Spinal Cord Compression and Recurrent Patellar Dislocation

This 39-year-old man meeting DSM-IV criteria for schizophrenia, major depressive disorder, and mild to moderate intellectual disability was referred to a neurologist at age 32 years because of a progressive gait disorder.

His medical history revealed several falls that occurred periodically, beginning at age 12 years and associated with gait imbalance and lower extremity weakness. At age 31 years, he began feeling increasingly anxious when walking, and started using a wheeled walker. Problems with balance and lower extremity weakness worsened. He did not report urinary incontinence or sensory loss. He also suffered from recurrent patellar dislocation of the left knee. Family members noted spontaneous movements of the mouth. His medications included paroxetine (20 mg/day) and zuclopenthixol (6 mg/day).

At age 32 years, neurological examination showed facial muscle asymmetry and oral dyskinesia. Muscle tone and strength of the upper extremities were normal. There was weakness of the left quadriceps, and increased tone of the lower extremities, primarily left. Sensory function in all limbs was normal. Deep tendon reflexes were hyperactive but plantar responses were flexor. The neurologist was unsure if the man suffered from a pyramidal syndrome. A functional gait disorder was also considered. Additional neurological examination in the same year revealed hyperactive tendon reflexes with clonus in lower extremities, and a Babinski sign bilaterally. Cervical spine magnetic resonance imaging (MRI) showed basilar impression, with stenosis of the foramen magnum and compression of the spinal cord. Cervical traction therapy did not improve the position of the cervical spine. He underwent craniocervical decompression with occipitocervical spondylodesis. In the same year, he underwent a lateral release of the left patella and a tibial tubercle osteotomy. Seven years postoperatively (age 39 years), he walked without support with good balance and only occasional minor knee problems.

Patient 2: Clozapine-Induced Myoclonus

This 45-year-old man meeting DSM-IV criteria for schizophrenia and premorbid functioning categorized as mild intellectual disability suffered from diverse motor and neurological abnormalities associated with antipsychotic treatment, including myoclonic jerks of the face and limbs, rigidity, and tremors.

At age 20 years, he developed a chronic schizophrenia-like psychotic disorder with paranoid delusions. Subsequently, he was treated with various antipsychotics (levomepromazine, penfluridol, pimozide, olanzapine, and risperidone). Reasons for switching were unsatisfactory response, significant cogwheel rigidity, and akathisia. His cognitive abilities and adaptive behaviors deteriorated progressively. At age 37 years, he was given up to 700mg/day quetiapine. Subsequently, his parents noted attacks during which he screamed, his eyes rolled, and he grabbed his head. Seizures and oculogyric crisis were considered. During subsequent aripiprazole (15 mg/day) treatment, he had three generalized epileptic seizures. At age 40 years, his parents agreed to clozapine treatment. Clozapine was titrated upwards to 150 mg/day (mean plasma level = ~0.20 mg/L, therapeutic levels= 0.20–0.60

mg/L) and his cognitive abilities and adaptive behaviors stabilized. He was categorized as having moderate to severe intellectual disability.

After approximately three months of clozapine treatment, he demonstrated episodes of myoclonic jerks (sudden, brief, involuntary movements) of the face and upper limbs that lasted for approximately 1–60 sec, and occasionally caused falls. Total serum calcium and parathyroid hormone levels were repeatedly normal. Electroencephalography (EEG) analysis showed a mild irregular background pattern within normal limits and a few, predominantly isolated, spike-wave complexes. Some spike-wave complexes were indecisively synchronous with a jerk over the face. Clozapine was lowered to 125 mg/day and the myoclonic jerks nearly disappeared. However, psychotic symptoms and agitation prompted an increase of the dosage to 150 mg/day and the myoclonic jerks initially returned with the same intensity, supporting a diagnosis of clozapine-induced myoclonus. At age 45 years, he suffered from mild fluctuating myoclonic jerks, and minimal cogwheel rigidity and resting tremors bilaterally.

Patient 3: Parkinsonism

This 54-year-old man meeting DSM-IV criteria for schizophrenia (age at onset 26 years) and mild intellectual disability has shown mild parkinsonism (characterized by tremor, bradykinesia, rigidity, and postural instability) of unclear etiology with slow progression beginning at age 48 years. He had tardive dyskinesia, facial twitches of unclear etiology, and myoclonus of the left hand while treated with clozapine.

After responding insufficiently to other antipsychotics (haloperidol, chlorpromazine, and loxapine), and showing emerging signs of tardive dyskinesia (tongue, foot), he began clozapine at age 36 years (up to 300 mg/day), while also receiving benztropine (2 mg/day). He became less delusional, complained less of auditory hallucinations, and became more sociable and outgoing. Myoclonic jerks (not specified) and a seizure occurred in the sixth month of treatment. Tardive dyskinesia and myoclonic jerks markedly improved following discontinuation of benztropine, addition of clonazepam (3 mg/day), and reduction of clozapine dose (200 mg/day). At age 37 years, a physical examination revealed a mild hand tremor (unspecified). At age 38 years, clozapine was increased to 400 mg/day because of auditory hallucinations, temper outbursts, and irritability. Benztropine was added and clonazepam gradually tapered off, after which severe facial twitching was observed. Two tonic-clonic seizures attributed to clozapine led to temporary clozapine discontinuation at age 39 years. Clozapine was restarted at age 44 years, due to a failure to respond to olanzapine and quetiapine. He was treated with gabapentin (3000 mg/day) and clonazepam (1.5 mg/day) to prevent seizures. Despite the correction of hypocalcemia and hypoparathyroidism with calcium carbonate and vitamin D supplementation, he had facial twitches and a slight resting tremor.

At age 48 years, his schizophrenia was judged to be in fair remission but parkinsonism was noted, including hand tremor, cogwheel rigidity (left>right), and a slightly stooped posture with short steps. At age 51, hand tremor had progressed; neurological examination demonstrated mild parkinsonism and possible tardive dyskinesia with hypomimia (reduced facial expression/masked facies), frequent symmetrical facial twitches of unclear etiology,

bilateral action tremor (left>right) and an abnormal gait, leaning to the left, slightly stooped, with small steps, and little arm swing. MRI revealed significant brain atrophy and significant microangiopathic changes. Also at age 51, valproic acid was added to his medication because of irritability. Neurological evaluation at age 53 revealed frequent non-bothersome, small amplitude, myoclonus at rest in the left hand as well as mild rigidity in the right lower extremity and mild to moderate bradykinesia in all limbs (right>left). Unified Parkinson Disease Rating Scale motor subscale score was 22/108 with a diagnosis of mild stable parkinsonism of unclear etiology. Over the years, he showed a gradual cognitive and functional decline, becoming increasingly forgetful and needing more help in his activities of daily living. There was no family history of neurodegenerative disease and no pathogenic Parkinson disease-related genetic mutation [Butcher et al., 2013].

Patient 4: Postural and Action Tremor

This 30-year-old antipsychotic-medication-naïve woman with mild learning disabilities began showing signs of “shakiness” at age 20 years, clinically similar to essential tremor.

She was first seen by a neurologist at age 11 months relating to hypotonia and a mild delay in gross motor development. She received adequate levothyroxine, calcium carbonate, and vitamin D supplementation for hypothyroidism and hypocalcemia from age 10 and 20 years, respectively. At age 20 years, she was diagnosed with major depression and co-morbid anxiety disorder. She reported feeling “shakiness.” She commenced on citalopram (up to 30 mg/day) with good response. A mild right hand tremor (characteristics not further specified) was noted later that year. Chvostek sign was negative. At age 21, brain MRI showed mild hypoplasia of the inferior vermis with slight enlargement of the fourth ventricle. She was referred to a neurologist at age 26 years for worsening tremors that affected functioning at work. Muscle strength, tone, and bulk were normal in all limbs. Deep tendon reflexes were overall symmetrically hyperactive, with one or two beats of clonus at the ankles. She showed bilateral postural tremors (postural>action>rest tremor). The tremor was seen in all limbs (arms>legs, right>left) and head. There was a slightly decreased right arm swing. The primary differential diagnosis was between a levothyroxine-induced tremor and a postural and action tremor, clinically similar to essential tremor. There was no relationship between the levothyroxine dose and tremor severity. The tremors improved considerably on propranolol (40 to 60 mg/day). She had a 5 hr video-EEG at age 27 years that showed no correlation between the tremor and EEG findings. A recent worsening of the tremor was not improved by an increase of the propranolol, but was greatly improved by a change to gabapentin (400–600 mg/day). There was no family history of essential tremor or neurodegenerative disorders.

Patient 5: Intermittent Oculogyric Movements

This 38-year-old man meeting DSM-IV criteria for schizophrenia and mild intellectual disability developed persistent intermittent oculogyric movements while on olanzapine.

At age 21 years, he presented with psychotic symptoms including auditory hallucinations and delusions. Olanzapine 12.5 mg/day provided a good response, but within one month he had very mild extrapyramidal symptoms, including a mild decrease in facial expression,

slowness in movements, very mild rigidity, a mild decrease in pendular arm movement, and restlessness. After eight months of olanzapine treatment, periodic oculogyric movements were noted (~2–4 times per month). Nevertheless, he continued to receive olanzapine due to a good response. At the time of his last visit to the psychiatrist (age 38 years), medications included olanzapine (17.5 mg/day), fluoxetine (20 mg/day), domperidone (40 mg/day), calcium, and vitamin D, all for a prolonged period. His motor symptoms were assessed to be near previous observations, including some pill-rolling of the left thumb and occasional oculogyric movements managed with lorazepam as necessary.

DISCUSSION

These cases illustrate a wide range of co-morbid conditions that may underlie and influence the presentation of movement abnormalities in adults with 22q11.2DS (Table II), including congenital abnormalities, drug-induced motor side effects, and neurodegenerative processes. Although some reported movement abnormalities are relatively common findings outside the setting of 22q11.2DS, and a chance association is possible, physicians should be alert to treatable conditions that require specific diagnostic testing in order to identify optimal management.

Of the multi-system features associated with 22q11.2DS, congenital vertebral and skull base abnormalities are noteworthy in that they can, rarely, result in spinal cord compression [Konen et al., 2008; Hamidi et al., 2014]. Resulting secondary movement-related symptoms can include muscle weakness, hyperreflexia, stiffness, and coordination problems, which may require urgent medical attention. Arthritis may be a contributing factor. Radiological detection of cord compression is essential. We report here on a patient with basilar invagination, further complicated by recurrent patellar dislocation that is also a feature of 22q11.2DS [Bassett et al., 2011] (Patient 1), whose movement abnormalities resolved after appropriate surgical management of the primary problems.

Individuals with 22q11.2DS have an increased vulnerability to seizures that may be “idiopathic” and/or related to hypocalcemia, hyperprolinemia, fever, ischemia/hypoxia, or concomitant medication, especially psychotropics [Kao et al., 2004; Cheung et al., 2014]. Two of our patients exhibited seizures, following antipsychotic medications (Patients 2 and 3). Clozapine-induced myoclonus (Patients 2 and 3) may be epileptic (cortical origin) or could be subcortical in origin (i.e., non-epileptic), or a combination. The multifocal nature of the jerks is suggestive of subcortical origin. However, some facial myoclonus in Patient 2 was possibly related to spike and waves on the EEG. Therefore, an epileptic (cortical) onset cannot be ruled out. Further studies will determine whether, as suggested by these cases and previous reports (e.g., [Krahn et al., 1998]), individuals with 22q11.2DS may be especially prone to experience seizures with antipsychotics [Butcher et al., in press].

Antipsychotics may cause or aggravate movement disorders in 22q11.2DS, including parkinsonism (Patients 2 and 5), akathisia (Patient 2), dystonia (Patient 5), and dyskinesia (Patients 1 and 3). Strikingly, two patients (Patients 2 and 3) showed parkinsonism while receiving clozapine; a side effect assumed to be (near) absent in clozapine treatment [Seeman, 2014]. Moreover, one patient developed oculogyric crises while receiving

olanzapine (Patient 5) and another (Bassett et al., 2011) on quetiapine; this is an extremely rare side effect of these medications [Bavle and Kumar, 2013]. Our clinical experience suggests that patients with 22q11.2DS might be more prone to develop antipsychotic-induced movement disorders, including those associated with other psychotropic medications such as (mood-stabilizing) anti-epileptic drugs, lithium, and antidepressants [Haddad and Dursun, 2008]. Standard recommendations regarding treatment and caution with respect to extrapyramidal side effects, e.g. potential worsening of tardive dyskinesia with anticholinergics, should be followed.

There is increasing evidence that 22q11.2DS is associated with early-onset Parkinson disease [Butcher et al., 2013]. For that reason, it is essential that individuals with 22q11.2DS are monitored for the development and progression of parkinsonism. Distinguishing antipsychotic-induced parkinsonism and Parkinson disease, the most common neurodegenerative cause of parkinsonism, may present a particular challenge in clinical practice. Specifically, clinicians may attribute symptoms incorrectly or exclusively to antipsychotic medications, while in fact there is Parkinson disease; thus delaying diagnosis of this treatable condition. When parkinsonism occurs, expert neurologic consultation should be sought. Molecular imaging of the presynaptic nigrostriatal dopamine system, where available, should be considered [Catafau and Tolosa, 2004; Booij et al., 2010].

The endocrine abnormalities associated with 22q11.2DS may exacerbate, or result in, movement abnormalities. In addition to an increased risk of seizures, symptoms of hypocalcemia include tetany, muscle cramps, and tremors [Weinzimer, 2001; Cheung et al., 2014]. Tremors are common in thyroid dysfunction and its treatment. Standard investigations and management should help to exclude endocrinological factors [Bassett et al., 2011].

The clinical complexity of 22q11.2DS may present significant challenges to diagnosis and optimal management. In clinical practice, it is not always possible to readily discern the 'key clinical findings' from the 'additional, secondary or minor movement abnormalities' impacting symptoms. Clinical assessments of movement abnormalities are subjective and motor abnormalities can be over- and under-rated. Different clinical conditions may lead to identical symptoms, but require targeted medical attention. Assessment may be further hindered by learning difficulties and psychiatric illness. For example, anxiety [Fung et al., 2010; Schneider et al., 2014] may color the clinical presentation. There is a potential for physical illnesses related to structural or neurodegenerative processes to be misdiagnosed as "functional" disorders (Patient 1). Especially early on, it may not be possible to distinguish conditions. The principal underlying cause may only be revealed after careful clinical monitoring (Patient 3). Interventions must be targeted to best suit the presumptive diagnosis, with successive trials of treatment using established goals for endpoints and periodic reassessments. If drug treatment is indicated, it is important to ensure a "start low, go slow" approach, as generally applicable for geriatric patients and patients with intellectual disabilities.

In light of the apparently enhanced vulnerability in 22q11.2DS, movement abnormalities in this population are yet understudied. One study reported that adult 22q11.2DS patients with

schizophrenia performed worse than those without schizophrenia on tests of manual dexterity, though on average all patients performed far below the norm [Chow et al., 2006]. Notably, in patients with idiopathic schizophrenia motor symptoms are found in medication-naïve first-episode patients and in those at risk for psychosis [Koning et al., 2010]. However, it is not possible to predict on an individual basis who will develop a psychotic disorder, including 22q11.2DS patients who are at 25% risk. Motor symptoms may be candidates for inclusion in prediction algorithms, opening up avenues for early detection of psychotic disorders. Recent evidence suggesting that 22q11.2DS is a genetic risk factor for early-onset Parkinson disease [Butcher et al., 2013] further indicates the potential for 22q11.2DS as a model for understanding the underlying pathophysiological processes for a broader array of neuropsychiatric and neurologic conditions.

In conclusion, further knowledge about movement abnormalities in adults with 22q11.2DS will assist medical practitioners in improving the clinical care of this growing patient population. Systematic studies are needed to better characterize the spectrum of movement abnormalities in the adult 22q11.2DS population. The results promise to help determine whether subclinical motor and other symptoms may be predictors of treatable neuropsychiatric and neurodegenerative diseases in later life, and could help in understanding mechanisms of disease applicable to these common disorders in the general population.

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Reported Movement Abnormalities in Five Adults With 22q11.2 Deletion Syndrome

TABLE 1

Pt	Sex	Age ^a	Psych ^b	Movement abnormalities, including seizures	Differential diagnoses
1	M	39(29)	SCZ, MDD	Gait disorder ^c Spontaneous movements of the mouth	Spinal cord compression and patellar dislocation ^d , functional gait disorder Tardive dyskinesia
2	M	45(37)	SCZ	Jerks in face and limbs ^c Eye-rolling, head grabbing Tonic-clonic seizures Cogwheel rigidity, tremor Restlessness	Clozapine-induced myoclonus ^d , hypocalcemia Antipsychotic-induced seizures, oculogyric crises Antipsychotic-induced seizures, 22q11.2DS-related seizures Parkinsonism related to 22q11.2DS, clozapine-induced parkinsonism, Parkinson disease Akathisia
3	M	54(36)	SCZ	Bradykinesia, rigidity, tremor, stooped posture, hypomimia ^c Myoclonic jerks Tardive dyskinesia (tongue, foot: not specified) Tonic-clonic seizures	Parkinsonism related to 22q11.2DS ^d , Parkinson disease Clozapine-induced myoclonus, 22q11.2DS-related myoclonic epilepsy, tardive dyskinesia Antipsychotic-induced tardive dyskinesia (worsened by benzotropine) Clozapine-induced seizures, hypocalcemic seizures, 22q11.2DS-related seizures
4	F	30(21)	MDD, AD	“Shakiness”, hand tremor ^c	22q11.2DS-related postural and action tremor ^d , drug-induced tremor
5	M	38(19)	SCZ	Recurrent involuntary upward deviation of the eyes ^c Hypomimia, decrease in arm-swing, slowness, rigidity	Olanzapine-induced oculogyric crises ^d , tardive dyskinesia Antipsychotic-induced parkinsonism

Pt, patient; M, male; F, female

^aCurrent age (22q11.2DS age at diagnosis) in years

^bPsychiatric diagnoses (DSM-IV). SCZ, schizophrenia; MDD, major depressive disorder; AD, anxiety disorder

^cKey clinical findings as described in clinical reports that prompted neurological consultation

^dMost probable cause(s) of the described movement abnormalities

TABLE II

Co-Morbid Conditions in 22q11.2 Deletion Syndrome Associated With Movement Abnormalities

Co-morbid conditions	Rates ^a	Clinical implications
Congenital abnormalities		
Craniocervical spine anomalies	NA ^b	Cervical traction therapy, neurosurgery if applicable
Patellar dislocation	10%	Orthopedic surgery as applicable
Seizures	40%	
"Idiopathic" epilepsy	5%	Anti-epileptic medications
Hypocalcemic seizures		Vitamin D and calcium supplementation
Drug-induced seizures		Adjust dosage, reconsider medication choice
Other (e.g. fever, ischemia/hypoxia)		As applicable
Psychiatric co-morbidities and treatments	60%	
Psychotropic medication (e.g. antipsychotics)		Adjust dosage, reconsider medication, "start low, go slow" dosing approach
Parkinson disease	NA ^c	Dopaminergic therapy; careful balancing with antipsychotics if applicable
Endocrine related diseases		
Hypocalcemia	>60%	Vitamin D and calcium supplementation
Thyroid dysfunction and/or treatment	25%	Adjust treatment

^aRates are approximate estimates of prevalence in adulthood [Bassett et al. 2005; Bassett et al. 2011]

^bWhether these anomalies contribute directly to spinal cord compression/greater instability in 22q11.2DS adults has not been investigated

^cAge dependent penetrance; e.g. ~6% over the age of 30 years [Butcher et al. 2013]

NA, not applicable