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Brief Reports

Clinical Characteristics of 49 Patients with Psychogenic Movement Disorders in a Tertiary Clinic in Turkey

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Abstract: **Patients admitted to movement disorders outpatient unit at a university hospital between January 2002 and June 2007 were screened for psychogenic movement disorders (PMDs). Out of 1,743 patients, 49 patients (2.8%), including four children, were diagnosed to have PMDs. Women to men ratio was 34/15. The mean age and the age-at-onset were 41 ± 17 years and 36 ± 15 years in the adult group, and 10 ± 2 and 9 ± 2 years in children. Among the whole group, 44% had tremor, 24% dystonia, 12% pure gait disorders, 8% parkinsonism, 6% chorea-ballism, and 4% tic disorder. PMD developed acutely in 85% of patients, and distractibility was observed in 83%. Of the patients, 81% met the criteria for clinically established PMD, whereas 16% for documented and 2% for probable PMD. Although our data was obtained from a different culture, our results showed that hospital-based frequency and phenomenological features between our PMD group and previously reported ones are similar.** © 2009 Movement Disorder Society

Key words: Psychogenic movement disorder; tremor; dystonia; parkinsonism; chorea; gait disorder

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Psychogenic movement disorders (PMDs) are not uncommon in movement disorder clinics.[1] PMDs may phenomenologically mimic almost all movement disorders. The most common movement disorder is tremor, followed by dystonia and others.[2–5]

Diagnostic criteria for PMDs was first identified by Fahn and Williams, based on atypical and common clinical clues.[6] Later, other authors described additional features to distinguish PMD patients from those with neurogenic movement disorders.[7–9]

Because there is no study written in English on any hospital-based data of PMDs in Turkey, we aimed to identify the frequency and phenomenological features of PMDs in our patient population with movement disorders.

PATIENTS AND METHODS

Patients admitted to our Movement Disorders Unit between January 2002 and June 2007, were screened for PMD by one of the three movement disorders specialists participating in this study (S.E., G.K., S.Ö.), based on the criteria for PMD.[6–9] In case of any doubt in diagnosis, another colleague in our team evaluated the patient independently. Written informed consent was obtained from all PMD patients except two.

Several characteristics of PMDs such as phenomenology, distractibility, coactivation sign, and uneconomic postures were noted. Distractibility was considered if PMD symptoms had abated or ameliorated when patients concentrated on mental or complex motor tasks.[7–11] Coactivation sign is characterized by appearance or disappearance of enhanced muscle tone in the presence or absence of tremor respectively, as described by Deuschl and coworkers.[8] Patients were categorized into four groups according to the criteria proposed by Fahn and Williams (Table 1).[6] An experienced psychiatrist (T.E.) evaluated patients by clinical interview according to the DSM-IV criteria.

RESULTS

Among 1,743 patients with movement disorders, 49 patients (2.8%) were diagnosed as PMDs. Four patients were children, of whom, one with tremor and the other

TABLE 1. *Diagnostic criteria for psychogenic dystonia (Fahn and Williams, 1988)*[6]

Degree of diagnostic certainty	Criteria
Documented	Persistent relief by psychotherapy, suggestion or placebo, or observed without the movement disorder when "unobserved"
Clinically established	Incongruent with classical dystonia or inconsistent plus other psychogenic signs, multiple somatizations or obvious psychiatric disturbances
Probable	Incongruent or inconsistent OR psychogenic signs or multiple somatizations
Possible	Evidence of emotional disturbance

with gait disorder were reported previously.[12] Characteristics of patients are summarized in Table 2. Out of 49 patients, 34 (69.4%) were female. The duration of symptoms was longer than 3 years in 19 patients (38.7%) and longer than 20 years in 3 (6.1%). Tremor was the most frequent symptom, followed by dystonia and the others. Bradykinesia in patients with Parkinsonism was distinguished from Parkinson's disease (PD) by atypical characteristics. One of them exhibited exaggerated slowness on one side during finger tapping with each hand separately, which disappeared when she finger tapped with both hands simultaneously. Another patient had slowness resembling slow motion picture and robot like abnormal gait. She was on levodopa for 8 years with a misdiagnosis of PD. Her symptoms improved by levodopa (Madopar caps.) as well as placebo (caps.) given for 3 weeks.

Out of 6 patients with pure gait disorder, 4 exhibited buckling in the knees, one had springing gait with exaggerated arm swing and one shuffling gait. Eighteen patients (36.7%) had multiple movement disorders. Coactivation sign was positive in all patients with tremor. Twenty-one patients (42.8%) exhibited give-way weakness, 19 (38.7%) nonanatomical sensorial disturbances, 14 (28.6%) uneconomic posture, 4 (8.2%) bizarre speech, and 4 (8.2%) pseudo-seizures.

Forty-one patients (83.7%) reported a precipitating factor, such as death of a relative, marital problems, poverty, unemployment, etc. Two patients developed their symptoms following the deaths of their brothers under the terrorist attacks while performing their military service. Six women and adolescent girls in our series had been exposed to domestic violence. A history of exposure to a disease model was noted in 19 (38.7%) patients. Psychiatric examination revealed that 16 (32.6%) patients had major depression, 8 (16.3%) anxiety disorder, and 2 (4%) residual schizophrenia. Symptoms of 44 (89.8%) patients were correlated with conversion disorder, 4 (8.2%) of malingering, and 1 (2%) of factitious disorder with predominantly physical symptoms.

Only 26 patients were followed-up for a period between 15 days and 24 months. Twelve patients including four children showed clinical improvement. Age-at-onset of these patients was 7 to 37.5 years, except 2 patients who first showed their symptoms at 50 and 70 years of age. Disease duration varied between 10 days and 8 years.

Illustrative Cases:

Patient 1

A 16-year-old woman presented with a 1-year history of tremor on four extremities abated with distraction. Her gait was dance-like and featured scissoring associated with irregular tremor of the trunk and legs punctuated by falls without injury. She also exhibited uneconomic postures (Video Segment 1). Psychogenic tremor and gait disorder were suggestive of clinically established form.

TABLE 2. *Demographic and clinical features of 49 patients with PMDs*

Female/male ratio	34/15
Mean age (yr)	
All patients (n = 49)	39.0 ± 18.7 (range: 8–86)
Adults (n = 45)	41.5 ± 17.4 (range: 15–86)
Children (n = 4)	10.0 ± 1.9 (range: 8–12)
Mean age at onset (yr)	
All patients (n = 49)	33.7 ± 17.2 (range: 7–65)
Adults (n = 45)	36.9 ± 15.9 (range:15–65)
Children (n = 4)	9.2 ± 2.2 (range: 7–12)
Duration (months)	53.0 ± 88.1 (range: 10 days–36 yr)
Type of movement disorder	
Tremor	22 (44.8%)
Dystonia	12 (24.4%)
Gait disorder	6 (12.3%)
Parkinsonism	4 (8.2%)
Chorea/ballism	3 (6.1%)
Tics	2 (4.0%)
Abrupt onset	42 (85.7%)
Distractibility	41 (83.6%)
Psychiatric illness	26 (53.0%)
PMD diagnostic classification	
Documented	8 (16.3%)
Clinically established	40 (81.6%)
Probable	1 (2.0%)

Values are mean ± SD or n (%).
PMDs, Psychogenic movement disorders.

Patient 2

A 44-year-old woman had an 8-year history of inconsistent tremor, speech disorder with intermittent pauses interrupting the fluency, and irregularly lengthening or shortening of the syllables. Her gait was stiff-legged accompanied by a give-way weakness, which improved with distraction (Video Segment 2). Psychogenic tremor, speech, and gait disorder were suggestive of clinically established form.

Patient 3

A 16-year-old woman with a residual right hemiparesis demonstrated synchronized ballistic movements accompanied by a hopping gait on her left foot, which improved with distraction (Video Segment 3). Psychogenic gait disorder and ballismus were suggestive of clinically established form.

Patient 4

A 25-year-old man had a 3-year history of continuous tremor of the legs and a 1-year history of camptocormia associated with slowness of movement, which disappeared with distraction (Video Segment 4) and while he was unaware of being watched. He was diagnosed to have documented psychogenic tremor and parkinsonism.

Patient 5

An 8-year-old boy had buckling of his legs during walking for 1 year. His symptoms evoked upon suggestion that he outstretch his arms until he was tired. These abnormalities always occurred while he was close to a chair or a wall without causing falls (Video Segment 5). His psychogenic gait disorder was consistent with clinically established form.

DISCUSSION

Out of 1,743 patients with various movement disorders seen in a 5.5 year-period, 2.8% were diagnosed as PMD. This rate was similar to the results reported previously which varied between 2.5% and 4.1%.[2,5] Our results were also consistent with other studies, in which tremor was found to be the predominant form of PMD, followed by dystonia, in both adults[3,5,13] and children.[14] In our series, phenomenologic features of psychogenic tremor in two children and two adolescent patients were similar to those noted in adults. Baik and Lang reported that the patients having gait disorders associated with other types of PMD exhibited slowness of gait, while those having pure psychogenic gait disorder showed "buckling of the knees" pattern.[15] Of our 6 patients displaying pure gait disorder, 4 exhibited buckling of the knees. Phenomenological features between adult and child patients differed in gait pattern; two children with pure gait disorder exhibited buckling of the knees and two adolescent patients displayed dance-like bizarre and hopping gait, whereas adult patients had either slow or stiff-legged gait pattern, some of whom also had other types of PMDs.

In our PMD group, women predominance[3-10,15] and mean age-at-onset was compatible with the previous series.[2,3,7,8,10,15]

The abrupt onset of symptoms, which support the diagnosis of PMD,[2,5,8,10,11] was noted in the majority of our patients and distractibility was observed in 83%. According to the criteria of Fahn and Williams,[6] 81% met the "clinically established," 16% "documented," and only 2% "probable" PMD, compatible with Baik and Lang's series.[15] According to the DSM-IV criteria, the majority of our patients had conversion disorder, as in the other series.[2,5,8]

One of the major difficulties associated with the management of PMD is the high rate of drop out of these patients in follow-up compared to patients with other chronic movement disorders such as PD. Since patients with PMD are reluctant to accept this diagnosis, they tend to change their physician in an attempt to seek another diagnosis which might support their expectations. In the presented series, only 26 patients were followed up for limited periods, and 12 of them exhibited clinical improvement. Deuschl and coworkers reported that the clinical course was not benign on the basis of a mean of 60-month follow-up period of 16 patients with psychogenic tremor.[8] In addition, the response to treatment is usually poor and symptoms may persist even up to 20 years in more than 90% of patients.[2,6,7] Young subjects were found more likely to recover than older patients.[8] Especially children with acute onset and short duration of disease appeared to have the best prognosis.[14] In accordance with these observations, all children and six young-onset adult patients in our series completely recovered.

There are some limitations in this study. Our population size is relatively small and follow-up data is limited. The rate of 2.8% of PMDs in the pool of all movement disorders in our center may not reflect the actual frequency of the PMDs in all tertiary referral centers in our country, because many of these patients refer to our outpatient clinic after being evaluated and even correctly diagnosed in other tertiary referral centers.

In conclusion, although our patients are from a different culture, and some culture specific features may play a role in the development of PMD, most of the precipitating factors and symptoms are similar to those seen in different cultures reported in the literature.

LEGENDS TO THE VIDEO

Segment 1. Patient 1 demonstrated inconsistent tremor of four extremities, uneconomic postures, and dance-like gait associated with falls.

Segment 2. Patient 2 had tremor of both hands, slowness of movements, and stiff-legged gait.

Segment 3. Patient 3 demonstrated abnormal ballistic movements and a hopping gait on her left foot.

Segment 4. Patient 4 had asymmetric tremor of the legs, slowness of movements, and camptocormia.

Segment 5. Patient 5 had buckling of the legs during walking when he felt tired.

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The Duration of the Motor Response to Apomorphine Boluses Is Conditioned by the Length of a Prior Infusion in Parkinson's Disease

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Abstract: **"Pulsatile" administration of levodopa has been invocated a relevant factor for motor fluctuations in Parkinson's disease (PD). We studied dopaminergic sensitivity to apomorphine in 10 parkinsonian patients with motor fluctuations. Patients were tested as follows: the minimal effective dose of apomorphine (MED-1) was administered in the morning to induce an *on* response. Fifteen minutes after this motor response had disappeared, an apomorphine infusion was initiated and maintained to ensure *on* periods of three different durations on different days. Infusion lasted for ¯30, 60 and 90 minutes. Subsequently, the infusion was stopped, and after 15 minutes in the *off* state, a second bolus of apomorphine (MED-2) was given. The mean infusion doses were 49.2 ± 5.4, 108.4 ± 10.3, and 150 ± 8.2 mg. These elicited *on* periods of 48.2 ± 4.1, 110 ± 4.5, and 195 ± 3.8 minutes. The MED-2 elicited *on* responses with a duration of 30 ± 4.5, 18.4 ± 3.2, and 11.2 ± 4.1 minutes. The duration of the *on* response induced by the apomorphine infusions correlated inversely ($P < 0.01$) with the *on* induced by the MED-2 of apomorphine. Our findings indicate that a continuous dopaminergic stimulus may induce pharmacodynamic changes associated with tolerance in PD patients.** © 2009 Movement Disorder Society

Key words: apomorphine boluses; apomorphine infusion; motor complications; pharmacological tolerance

Daily fluctuations of motor performance in patients with Parkinson's disease (PD) treated chronically with levodopa (L-dopa) still represent a major clinical and therapeutic challenge and an unresolved pathophysiological issue.[1,2] The "wearing-off" phenomenon and

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dyskinesias are highly prevalent in the general PD population.[3] Peripheral L-dopa pharmacokinetics is not primary to the development of the "wearing-off."[4] Thus, central pharmacokinetic mechanisms such as reduced capacity of nigrostriatal pathway to store dopamine,[4,5] and pharmacodynamic changes due to modification of striatal dopamine receptors are considered in the development of motor complications.[2,6,7] Positron emission tomography using the D-2 receptor ligand raclopride has failed to demonstrate a significant modification in the number of dopamine receptors in untreated PD patients.[8] Thus, putative modifications of striatal dopamine receptor function and responsiveness associated with the development of motor complications in PD may be related, at least in part, to the standard pattern of administering L-dopa.[9,10] Indeed, a wealth of experimental and clinical data has been gathered in recent years indicating the importance of the pattern of drug delivery and receptor stimulation (pulsatile vs, continuous) in order to restore more efficiently dopamine deficiency in PD.[3,10,11–13] This is emphasized by a growing sensitivity to apply the concept of continuous dopaminergic (DAergic) stimulation in clinical practice[3,14] and a parallel pharmaceutical development of long-acting DAergic drugs. However, continuous delivery of DAergic drugs may not necessarily restore the physiological effect of dopamine in the denervated striatum and, indeed, could be associated with tolerance,[3,10,15] potentially risking its therapeutic value. We now report how the duration of the *on* motor response induced by apomorphine infusions of different length may change the capacity of dopamine receptors to further stimulation.

PATIENTS AND METHODS

After informed consent was obtained, 10 patients (7 males and 3 females) with PD (mean duration of illness: 12.4 ± 3.1 years), chronically treated with L-dopa (mean treatment duration 10.2 ± 1.4 years), were admitted to hospital for the study. Patients also received treatment with dopamine agonists (bromocriptine, pramipexole, and ropinirole). All patients suffered motor fluctuations and dyskinesias. Eight patients showed a "wearing-off" pattern of fluctuations. Two patients had complex *on–off* fluctuations. Dyskinesias when *on* were present in all 10 patients; *off* period dystonia was present in 4 patients, and diphasic dyskinesias in 2 patients.

Pharmacological Tests

All patients received domperidone (60 mg/day, p.o.) for at least 3 days before the study and during the infusions. The minimal effective dose (MED) of apomorphine for every patient was defined as the amount necessary to reduce by 60% or more the disability score of the Unified Parkinson Disease Rating Scale (UPDRS part III) for a minimum stable period of 10 minutes.[16] Tests were conducted in the morning after at least 12 hours without antiparkinsonian medication during consecutive days. The MED was defined by trial and error prior to the initiation of the study as described earlier.[16] During the study, patients received apomorphine in the following sequence: the MED of apomorphine (MED-1) was administered in the morning to induce an *on* response. Fifteen minutes after this motor response had disappeared, as judged by a return to the baseline *off* state, an apomorphine infusion was initiated and maintained to ensure *on* periods of three different durations on different days. For this purpose, apomorphine infusion was given for ˜30, 60, and 90 minutes. The infusion was then stopped, and the patient's status was monitored until the motor state returned to the basal *off* situation. After a period of 15 minutes in the *off* state, a second bolus of apomorphine (MED-2) was given, and the magnitude and duration of the response were assessed as mentioned earlier.

The UPDRS part III and tapping tests of the limbs were used for clinical assessment. The tapping tests consisted in measuring the time required to touch 50 times, two points separated 50 cm for the upper limbs, and 25 cm for the lower limbs over a maximal observation period of 300 seconds. The *on* pharmacological state was defined as a minimum 60% or 25% improvement over baseline values of either the UPDRS part III or tapping tests for a minimum stable period of 10 minutes.

Data were statistically analyzed data by analysis of variance. The relationship between duration of the *on* induced by the infusion and the second Apo bolus (MED-2) was studied by linear regression analysis.

RESULTS

The mean MED of apomorphine was 4.2 ± 1.2 mg. On the third day, the MED produced a stable motor response with a duration of 45.2 ± 16.4, 40.3 ± 4.5, and 43.4 ± 3.2 minutes (see Fig. 1). The *on* period scores as evaluated by improvement in the UPDRS and tapping tests did not vary significantly throughout the three different study days for each individual patient. The mean UPDRS part III when *off* was 60.3 ± 4.1 and when *on* 20 ± 4.1. Tapping tests for the upper limbs improved significantly from 130 ± 16.4 minutes when *off* to 48.4 ± 5.6 minutes when *on* and

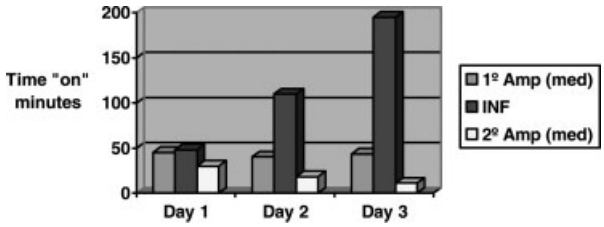

FIG. 1. Response modification for previous *on* duration.

for the lower limbs from 85.8 ± 12.4 to 40.2 ± 9.3 minutes. The mean infusion doses were 49.2 ± 5.4, 108.4 ± 10.3, and 150 ± 8.2 mg during 30, 60, and 90 minutes, respectively. These elicited *on* periods of 48.2 ± 4.1, 110 ± 4.5, and 195 ± 3.8 minutes. The responses to the second boluses of apomorphine (MED-2) were, respectively, 30 ± 4.5, 18.4 ± 3.2, and 11.2 ± 4.1 min. Thus, the duration of the *on* response induced by the apomorphine infusions correlated inversely ($P < 0.01$) with the *on* induced by the MED-2 of apomorphine.

The MED-1 of apomorphine induced *on* periods that were significantly ($P < 0.01$) more prolonged than the ones elicited in response to the MED2 (see Fig. 1) for every study day. No statistical difference was found in the latencies of the *on* responses elicited by the MED-1 and MED-2.

DISCUSSION

We observed a reduction in the response to the MED of apomorphine after apomorphine infusions that induced successively longer *on* periods. In keeping with previous studies in patients with PD[16] and 1-methyl-4-phenyl-1,2,3,6-tetrayhydropyridine intoxicated monkeys,[17] the first apomorphine pulse induced the longest motor improvement. The most interesting finding of our study is the relation between the duration of the *on* period induced by a relatively short infusion of apomorhine and the response to a second (test) bolus of apomorphine (MED2). This could be directly related with the "post-on" worsening of motor scores documented in PD.[18] Such phenomenon may be very intense and clinically relevant in some particular patients who developed a severe worsening of the parkinsonian state, once the effect of L-dopa has waned ("super-off"). We observed a somehow similar deterioration in the capability to respond but in direct relation with the duration of the apomorphine infusion. The reduction in responsiveness to apomorphine reported here may depend upon functional changes in the striatum itself or the striatopallidal pathways.

One possibility is that apomorphine would stimulate the remaining DAergic presynaptic terminals to reduce dopamine release,[19] a well-established mechanism experimentally. Then, following rapid interruption of the infusion, the striatum would be rendered with further DAergic depletion and less capability to respond to the next bolus. It would be like a shift in the dose–response curve to the right. In keeping with this is the observation that the sensitivity to apomorphine doses is reduced and associated with a reduction in the motor improvement observed clinically only when threshold doses are used.[20,21] On the contrary, repeated administrations of apomorphine at doses well above the *on* threshold are not associated with tolerance.[22,23] On the other hand, long-term infusions of L-dopa, apormorphine, or lisuride are generally associated with a robust therapeutic benefit,[24–26] and if anything, when the infusions are stopped overnight, movement capacity seems to improve.[27]

Another complementary possibility to explain our findings may reside in that the short infusion modifies basal ganglia output activity to reduce its excitability once the DAergic stimulus quickly wears off. Juncos et al.[28] studied the effects of continuous and intermittent L-dopa treatment on behavioral and biochemical indexes in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal dopamine pathway. They demonstrated differential effect of continuous versus intermittent DAergic stimulation over glutamic acid decarboxylase activity in the output of the basal ganglia, and suggested that modification of neuronal systems located downstream from striatal dopamine receptors could be responsible for the reduction in motor response observed with discontinuous administration. Indeed, it now established that "pulsatile" administration of DAergic drugs is associated with drastic changes in basal ganglia output (i.e., STN, subthalamic nucleus; GPi, globus pallidus pars interna) activity.[26] These are characterized by a shift from neuronal firing hyperactivity in the parkinsonian state to a marked drop in firing rate in the *on* dyskinetic state[29–32] and a concomitant change from predominant beta band oscillatory activity to theta and gamma bands activity.[33] In both *off* and *on* medication states, the basal ganglia output nuclei are not normally operating, and compensatory mechanisms intervene to modify neuronal activity in the opposite direction. In the normal state, neuronal activity (ratio GPe/GPi), as judged by the expression of citocrome oxidase, glutamic acid decarboxylase and firing rate[34,35] is around 1 ± 0.1,[36] in the parkinsonian state is reduced (mainly due to increased GPi activity), and in the *on* dyskinetic state it is increased well above 1.[36] This implies a functional imbalance within the basal ganglia that may render the system less sensitive to respond immediately after cessation (i.e.

apomorphine infusion) of the *on* period. Cederbaum et al.[37] suggested that the striatum may need a time of "rest" to restore DAergic responsiveness. In fact, nowadays parkinsonian patients are treated with subcutaneous apomorphine or lisuride infusions which are discontinued overnight.[25,27] This may explain the lack of tolerance to apomorphine seen in long-term studies.

In conclusion, our results suggest that, in PD patients with severe motor complications perhaps, a prolonged stimulus may not be sufficient to control DAergic deficiency because of the potential occurrence of tolerance. This may have practical therapeutic implications for the development of newer drug delivery and other therapeutic approaches aiming to restore DAergic deficiency in PD.

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Contrast Sensitivity in Parkinson's Disease Patients with Subthalamic Nucleus Deep Brain Stimulation

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Abstract: **This study examined whether deep brain stimulation (DBS) would affect the contrast sensitivity (CS) curve in patients with PD. CS was tested in 12 nondemented PD patients treated with bilateral subthalamic nucleus DBS on and off stimulation and medications. Neither stimulation condition (on vs. off) nor medications altered CS performance in this group of patients. However, collapsed across conditions, patients with bipolar stimulation in this study had significantly poorer CS at higher spatial frequencies (12 and 18 cycles per degree) than patients with monopolar stimulation. This suggests that CS deficits in PD may possibly be influenced by DBS polarity and merits further study.** © 2009 Movement Disorder Society

Key words: Parkinson's disease; vision; contrast sensitivity; deep brain stimulation

Changes in visual contrast sensitivity (CS) are well-documented in PD.[1–6] Decreased sensitivity to middle and high spatial frequencies and increased sensitivity at low spatial frequencies have been reported in PD patients treated with dopaminergic medications.[1,4,5] Disrupted retinal dopaminergic transmission is one of the proposed mechanisms to explain CS deficits in PD patients because the CS curve normalizes with levodopa therapy.[1,3,7] However, CS impairments could also be due to dysfunction at higher levels of the visual system. Regan and Maxner[8] reported that PD patients demonstrated deficits in CS for stimuli in certain orientations. The visual system does not process orientation information at the level of the retina, suggesting involvement of later stages of the retinocalcarine pathway.[9] Furthermore, patients with lesions involving the occipital and parietal lobes also show reduced spatial CS.[10,11]

In this study, we examined whether deep brain stimulation (DBS) would affect the CS curve in patients with PD. The effect of DBS on CS has not previously been explored. If CS changes in PD are purely due to decreased dopamine in the retina, then DBS would not be expected to influence CS performance. In contrast, CS changes associated with DBS may provide further support for cortical involvement in PD-related CS impairment.

SUBJECTS AND METHODS

Twelve individuals (8 males, 4 females) with PD participated. All met CAPSIT-PD criteria for the diagnosis of PD,[12] and underwent DBS surgery because of dyskinesias and/or motor fluctuations despite optimal medical management. Inclusion criteria for the study were as follows: (1) Treatment with bilateral subthalamic nucleus (STN) DBS for at least 12 months, (2) MMSE score >24, and (3) no changes in stimulation or medications within the last 3 months. Five participants were being treated with monopolar stimulation, while seven had bipolar settings. Six were previously switched to bipolar from monopolar settings because of speech problems, and one was switched because of shoulder contractions. Participants signed an informed written consent, and research protocols were approved by an independent institutional review board.

Medical charts were reviewed to collect demographic variables such as age, duration of disease, gender, PD medications and doses, stimulator settings, and to rule out any systemic disorders that could potentially compromise vision. All participants were taking medications for their PD, and for ease of comparison, dopaminergic medications were converted into levodopa equivalent dosages (LEDs).[13]

Ocular health was obtained by a yes/no questionnaire asking for the presence of glaucoma, eye surgery, blindness, color blindness, retinal disease, or need for corrective lenses. None of the subjects had a history of glaucoma, color blindness, or retinal disease. Three participants had previous eye surgery, two for cataracts and one to correct diplopia at the age of 4. Participants who needed corrective lenses were allowed to wear them when testing visual acuity. The median binocular far visual acuity was 20/25 with a standard Snellen eye chart, and none of the participants had a visual acuity worse than 20/40.

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TABLE 1. *Demographic characteristics of PD patients*

	All (n = 12)	Monopolar (n = 5)	Bipolar (n = 7)	*t*-test	*P*-value
Age	61.3 (8.8)	60.0 (8.6)	62.1 (9.5)	−0.40	0.70
Gender	Males = 8	Males = 4	Males = 4	$X^2 = 0.69$	0.41
Far acuity (range)	20/15–20/40	20/15–20/30	20/15–20/40	$X^2 = 2.4$	0.66
Disease duration (years)	14.7 (7.1)	14.0 (6.2)	15.1 (8.1)	−0.26	0.80
Time since DBS surgery (months)	45.5 (21.3)	48.6 (22.5)	43.3 (22.0)	0.41	0.69
LED	700.1 (337.7)	667.6 (266.9)	723.2 (400.0)	−0.27	0.79
UPDRS motor					
DBS-on/meds-off	20.4 (7.2)	19.8 (8.1)	20.9 (7.0)	−0.24	0.81
DBS-off/meds-off	30.6 (10.3)	27.0 (10.1)	33.1 (10.3)	−1.02	0.33
DBS-off/meds-on	24.0 (10.4)	22.8 (11.1)	24.9 (10.7)	−0.32	0.75
DBS-on/meds-on	18.0 (7.9)	18.8 (10.4)	17.4 (6.5)	0.28	0.78
MMSE	28.3 (1.6)	28.8 (1.6)	28.0 (1.5)	0.87	0.41

Data expressed as mean (SD) unless otherwise noted.

All subjects were assessed by an unblinded rater in four different conditions using the Unified Parkinson Disease Rating Scale (UPDRS) motor section and the functional acuity contrast sensitivity test (FACT) (Sterero Optical, Chicago, IL).[14] Patients were evaluated in the morning in the medication-off state, at least 12 hours after their last medication dose. Because the majority of patients could not tolerate the DBS-off/medication-off state overnight due to severe parkinsonian symptoms, clinical assessments were made in the following fixed order: (1) DBS-on/medication-off, (2) DBS-off/medication-off, (3) DBS-off/medication-on, (4) DBS-on/medication-on. The DBS-on and off states were practically defined as 30 minutes after devices were turned on or off. The medication-on state was defined as the best clinical response to dopaminergic therapy.

Statistical Analysis

Demographic characteristics were compared with independent samples *t*-tests or chi-squares as appropriate. In order to evaluate the primary aim of this study, which was to examine whether stimulation improved CS scores in all patients, log transformed CS values for each participant were submitted to a repeated measures analysis of variance (ANOVA) with cycles per degree (CPD, 1.5, 3, 6, 12, 18) and Condition (DBS-on/medication-off, DBS-off/medication off, DBS off/medication on, DBS-on/medication-on) as the within subjects factors. A secondary aim was to examine the influence of polarity upon CS. Subjects were thus divided into two groups: those with monopolar stimulation only and those with bipolar stimulation (either bilateral bipolar stimulation or unilateral bipolar stimulation with contralateral monopolar stimulation). CS values from the FACT were submitted to a two-way mixed factorial analysis of variance with a within subjects factor of CS at each of the CPD and a between subjects factor of Polarity (monopolar and bipolar).

RESULTS

Demographic characteristics for the participants are listed in Table 1. The monopolar and bipolar groups did not differ in age, disease duration, levodopa dosage, UPDRS motor scores, MMSE, or visual acuity (Table 1).

There was a significant main effect of Condition on CS values ($F[3,33] = 3.2$, $P < 0.04$), though this appeared to be due to a learning effect, as CS improved from DBS-on/medication-off (Condition 1) to DBS-off/medication-off (Condition 2), with little change after the second exposure to the FACT. There was also a significant main effect of CPD on CS ($F[4,44] = 40.4$, $P < 0.0001$), which reflects the normal CS curve. Importantly, however, there was no significant Condition × CPD interaction ($F[12,132] = 0.50$, P = ns).

The analysis of polarity upon CS revealed a significant effect of Condition ($F[3,30] = 3.54$, $P < 0.03$) with improvement in CS from Condition 1 to Condition 2, and CPD ($F[4,40] = 52.01$, $P < 0.0001$), reflecting the normal CS curve. Overall CS performance, collapsed across all conditions, tended to differ between the monopolar and bipolar groups ($F[1,10] = 3.91$, $P < 0.08$), with the bipolar group having poorer CS scores (Fig. 1). While the interactions of Condition × CPD, Condition × Polarity, and Condition × CPD × Polarity were not significant (all Ps > 0.5), there was a significant interaction of CPD × Polarity ($F[4,40] = 5.78$, $P = 0.001$) (Fig. 1).

This significant interaction was explored with five post hoc *t*-tests. Collapsed across all conditions, the bipolar group demonstrated significantly poorer CS at

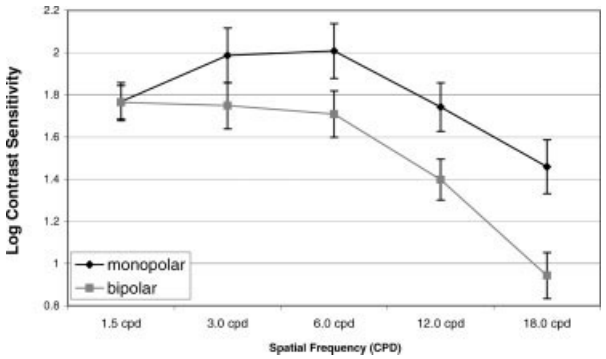

FIG. 1. Far functional acuity contrast sensitivity curves for the monopolar and bipolar groups collapsed across all conditions.

the 12 (t = 2.28, $P < 0.05$), and 18 CPD (t = 3.07, $P = 0.01$) and tended to perform more poorly at the 6 CPD (t = 1.75, $P = 0.10$).

DISCUSSION

CS values for this entire cohort of PD patients treated with chronic bilateral STN stimulation were not significantly different on or off stimulation or medication. However, patients with bipolar stimulation in this study had significantly poorer CS at higher spatial frequencies (12 and 18 CPD) than patients with monopolar stimulation. While this finding suggests that stimulation may affect CS, strong support of this conclusion was not found as there was no interaction of polarity and stimulation condition (on vs. off).

The limitations of this study should be kept in mind when interpreting these results. Our sample size was small and the study was unblinded. Ocular health was obtained by questionnaire, so we cannot completely rule out the presence or severity of cataracts, which can affect CS. We do not have preoperative CS values, so premorbid CS deficits are unknown. Our practically defined DBS-off state may have been too short. Approximately 75% of UPDRS motor score worsening occurs within 30 minutes after turning the stimulators off and 90% occurs over the subsequent 90 minutes.[15] While it would have been better to examine patients 2 hours after turning the stimulators off, many of our patients could not tolerate being "off" for that long, and we felt that 30 minutes was a reasonable compromise. Finally, we tested CS through the different conditions in a fixed sequence and found what appeared to be a strong learning effect from DBS-on/medication-off (Condition 1) to DBS-off/medication-off (Condition 2). An alternative interpretation would be that turning stimulation off improves CS, but CS performance did not decline again from DBS-off/medication-on (Condition 3) to DBS-on/medication-on (Condition 4). A randomly chosen order would have resolved this question, but could not be practically done in one testing session.

The reason why the monopolar group had better CS scores is unclear. Two of the patients in the bipolar group had 20/40 acuity compared to none in the monopolar group. However, there were no differences in overall visual acuity between the two groups. CS may be affected by the spread of the monopolar stimulation affecting the direct output from the basal ganglia to the parietal lobe. An alternate possibility is decreased clinical effect due to bipolar settings or suboptimal placement of the electrodes. Bipolar stimulation is used when monopolar stimulation causes side effects and requires higher voltages to achieve similar clinical benefits.[16] However, the UPDRS motor scores between the monopolar and bipolar groups were not significantly different suggesting that clinical effects were equal between the two groups. Unfortunately, there was no significant interaction of DBS/medication condition and polarity. Our study may have been too small to pick up such an interaction, but other factors such as pre-existing CS differences or other unknown clinical factors may be responsible.

In this study, medications did not affect spatial CS. Previous studies that demonstrated improvement in CS with levodopa used computerized methods.[3,7] We employed a standardized wall chart in this study, which might explain our results. It is also possible that postoperative medication reduction may be responsible for the lack of changes in CS performance, but one previous study found improvement in CS scores with a levodopa dose as low as 250 mg.[7] Further research will be necessary to clarify the combined effects of disease duration and medication dose on CS performance. Use of a sensitive computerized CS measurement is recommended.

We sought to ascertain whether DBS could affect CS performance in PD patients. The results of this study suggest that polarity of DBS possibly affects CS performance in patients with PD. Further studies with larger number of patients and a randomized testing order need to be conducted to evaluate our findings. Prospective studies evaluating CS before and after DBS surgery are also necessary to allow us to gain further insight into the contributions of medications, stimulation, and the surgery itself on CS performance in PD.

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Normal Interhemispheric Inhibition in Persistent Developmental Stuttering

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Abstract: **Imaging studies suggest a right hemispheric (pre)motor overactivity in patients with persistent developmental stuttering (PDS). The interhemispheric inhibition (IHI) studied with transcranial magnetic stimulation is an established measure of the interplay between right and left motor areas. We assessed IHI in 15 young male adults with PDS and 15 age-matched fluent-speaking subjects. We additionally studied the ipsilateral silent period (iSP) duration. We found no significant between-group difference for IHI or for iSP duration. We conclude that the interplay between the primary motor cortices is normal in patients with PDS. The abnormal right motor and premotor activity observed in functional imaging studies on PDS are not likely to reflect altered primary motor cortex excitability, but are likely to have a different origin.** © 2009 Movement Disorder Society

Key words: persistent developmental stuttering; transcranial magnetic stimulation; interhemispheric; transcallosal; ipsilateral silent period

Stuttering occurs in up to 5% of all children between 3 and 6 years of age. Later on, the vast majority of these children experience a spontaneous recovery. Stuttering persists after puberty only in about 1% of the general population, with a male to female ratio of about 4 to 1. This persistent developmental stuttering (PDS) has rather consistent core symptoms of repetitions and prolongations of phonemes as well as speech blocks. These primary symptoms are accompanied by variable secondary symptoms including grimacing,

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other movements, and avoidance behavior. Hereditary factors further influence the occurrence and the persistence of PDS.[1,2]

With the advent of structural imaging, several studies on adults with PDS provided evidence for a more variable gyrification in Broca's area (Brodman area 43/44),[3] less asymmetry of the Planum temporale,[3] and left Rolandic Opercular white matter disturbance.[4–6] In addition, functional imaging and magnetoencephalographic studies showed right sided overactivity of motor and premotor areas[7,8] and underactivity of auditory processing areas, particularly on the left side.[7,9] These functional imaging studies therefore partially confirmed hypotheses of abnormal lateralization of brain activity in PDS already proposed in the early 20th century.[10]

The right-hemispheric motor and premotor activity abnormalities could be causally related to stuttering,[11] or it could be compensatory for left-hemispheric structural problems.[4,8,12]

An established way to assess the transcallosal, interhemispheric interaction of primary motor cortices is the interhemispheric inhibition (IHI) measured by transcranial magnetic stimulation (TMS).[13,14] IHI determines the interplay between primary motor cortices. It is absent in children 4.2 to 5.7 years of age [15] and obviously develops thereafter, during an age known to be sensitive for speech development. IHI is altered in individuals with early musical training,[16] a condition known to share a similar time window to gain proficiency.[17–19] We hypothesized that IHI may be abnormal in adults afflicted with PDS. In particular, we expected the right hemisphere to be less inhibited, therefore reflecting the abnormally increased right hemispheric (pre)motor activity.

SUBJECTS AND METHODS

We investigated 15 male subjects with PDS and a mean age of 28.7 (standard deviation, SD 10.6) years. They were recruited from the Kassel stuttering therapy program of AvG and from the Göttingen stuttering self help group. Care was taken to exclude patients with cluttering, a rapid, erratic, and dysrhythmic speech dysfluency with distinct speech timing abnormalities coexisting with stuttering in some individuals.[20] All were right-handed with a mean Oldfield handedness score of 81.5 (SD 24.3) points. As healthy controls, we studied 15 subjects with no personal or family history of stuttering or cluttering and a mean age of 26.7 (SD 4.6) years, mean handedness score 88.3 (SD 22.5) points. None of the participants showed neurological or medical abnormalities on routine examination. None of the participants was taking CNS-active drugs at the time of the study. The protocol was approved by the ethics committee of the University of Göttingen, and written informed consent was obtained from all participants. At the beginning of the study, N.N., a speech language pathologist, or A.v.G., a physician who graduated in speech-language pathology, asked all participants to give a report of their current activities and of their history of speech dysfluencies. We used the stuttering severity index (SSI-3).[21] The speech sample contained a conversation about job or school and a reading task. The offline analysis of stutter-like dysfluencies included 500 syllables for the conversation and not less than 340 syllables for the reading task. Furthermore, the estimate of duration of the three longest blocks and observation of physical concomitants were included for PDS.

While the participants were sitting in a reclining chair, we delivered TMS over the optimal representation of the abductor digiti minimi muscle (ADM) of the dominant hand. Stimuli were generated by two Magstim 200 stimulators. One of them was connected to a figure-of-eight coil (outer diameter of each wing 7 cm), and the other was connected to a round coil (outer diameter 14 cm, all stimulators and coils from Magstim Company, Whitland, Dyfed, UK). Different coil sizes were used for easier placement of both coils on the head.[14] The figure-of-eight-coil was used for the conditioning pulse and held laterally, inducing a medially directed current flow in the brain. We used the round coil for the test pulse, it induced anteriorly directed pulses in the brain. We recorded MEPs from the ADM muscle bilaterally using silver-silver chloride electrodes in a belly-tendon montage and the "Signal" software with CED 1401 hardware (Cambridge Electronic Design, Cambridge, UK) at a sampling rate of 10,000 Hz, filtered at 1.6 Hz and 1 kHz. We also recorded 80 ms of prestimulus EMG in either channel to assess muscle relaxation. The test pulse was adjusted to yield contralateral amplitudes of about 1.0 mV, and the conditioning pulse to yield amplitudes of about 1.5 mV, with the subjects perfectly relaxed. Trials with imperfect muscle relaxation in the prestimulus recording were rejected. In random order, we studied interstimulus intervals of 2, 5, 6, 8, 10, 20, 50, and 80 ms 10 times each, and unconditioned test stimuli 20 times. Each side was investigated separately, and the amplitude of the motor evoked potential (MEP) recorded in the ADM contralateral to the test pulse was measured and normalized to the unconditioned amplitudes. The normalized MEP amplitudes were analyzed using a repeated-measure ANOVA with "intersti-

mulus interval" and "side" as within-group and "group" as between-group factors.

In addition, we used a one-coil technique over the hand area of one motor cortex during voluntary activation of the ADM muscle on either side. Here, a figure-8 coil was used over the optimal ADM representation, and stimulus intensity was adjusted to yield contralateral MEP amplitudes of about 2.5 mV contralaterally. The duration of the induced ipsilateral silent period (iSP) was obtained from 30 rectified and averaged trials as illustrated in Figure 2A. We measured the average baseline EMG amplitude in a time window of 75 ms of pre-TMS EMG recording. We determined the latency when the voluntary activity after the TMS pulse dropped below this baseline EMG level and the latency of any sustained recovery of EMG activity above this baseline EMG level, the latency difference providing iSP duration. Each side was investigated separately, and the data were analyzed using a repeated-measures ANOVA with "side" as within-group and "group" as between-group factors.

For overall stimulus intensity analysis, we cumulated all these intensity values in a single repeated-measures ANOVA with "group" as between-group factor and "hemisphere" as well as "task" (1.0 mV-rest; 1.5 mV-rest; 2.5 mV-activated) as within-subjects-factors. All results are indicated as mean value $\pm$ standard deviation, the level of significance was set at $P \leq 0.05$.

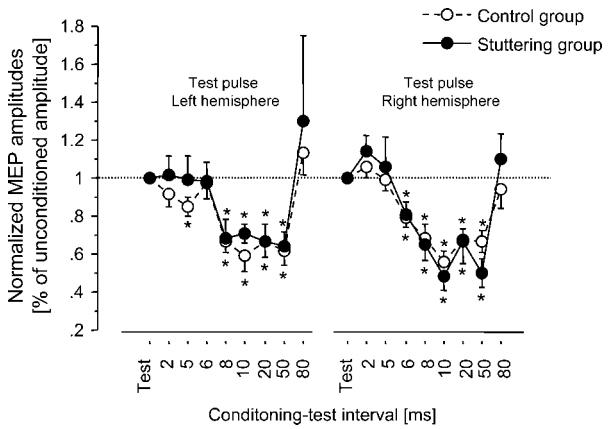

FIG. 1. Interhemispheric inhibition from a conditioning-test paired-pulse transcranial magnetic stimulation paradigm using 2 coils in 15 subjects with PDS and 15 age-matched controls. Conditioned motor evoked potentials are expressed in percent of the unconditioned response (dashed line). All symbols represent the mean $\pm$ standard error. Asterisks indicate a significant difference to the unconditioned test potentials.

RESULTS

Speech dysfluencies were more frequent in the stuttering subjects (14.95% SD 12.81%) than in the control subjects (0.42% SD 0.22%; unpaired, two-tailed *t*-test, $P < 0.001$). In the stuttering group, stuttering severity was classified as very mild in three subjects, mild in three subjects, moderate in two subjects, severe in three subjects, and very severe in four subjects according to the SSI-3.

For IHI there was no significant difference between groups for either hemisphere. The ANOVA indicated no effect of group [$F(1, 28) = 0.25$, $P = 0.62$], no effect of side, no interaction of side by group, an effect of interval [$F(8, 224) = 13.73$, $P < 0.0001$], and no overall interaction of side by interval [$F(8, 224) = 1.77$, $P = 0.085$]. The inter-stimulus intervals 5 ms and 6 ms yielded a more complex asymmetry of IHI. If the test pulse was on the left hemisphere, only the control group showed an early inhibition at the interval 5 ms, and no group showed any inhibition at the interval 6 ms. If the test pulse was on the right hemisphere, i.e., if the dominant left hemisphere inhibited the right hemisphere, the interval 5 ms did not yield an inhibition in any group, but the interval 6 ms induced a significant inhibition in both groups (Fig. 1). Finally, we observed an insignificant trend for facilitation at the interval of 2 ms in the stuttering group only.

For the iSP duration, a representative example is shown in Figure 2A. There was again no significant difference between groups [repeated-measures ANOVA, effect of group, $F(1, 27) = 0.85$, $P = 0.37$; Fig. 2B].

Stimulus intensities were not significantly different among groups. An exploratory ANOVA across different conditions and activation states indicated no effect of group [$F(1, 28) = 3{,}19$, $P = 0.085$], an effect of task [$F(2, 56) = 143.4$, $P < 0.0001$]. There was an interaction of task by group [$F(2, 56) = 29.0$, $P < 0.0001$], related to a slightly higher 1.0 mV intensity in the control group than in the stuttering subjects. In detail, the IHI test pulse intensity on the left hemisphere (right hemisphere) was 58.0 SD 9.4% (56.2 SD 10.1) in controls and 44.6 SD 7.3 (44.9 SD 6.7) in the stuttering group. The IHI conditioning pulse intensity on the left hemisphere (right hemisphere) was 44.2 SD 11.5% (43.9 SD 9.7) in controls and 38.4 SD 5.2 (41.3 SD 4.1) in the stuttering group. Finally, the test pulse intensity for iSP on the left hemisphere (right hemisphere) was 31.5

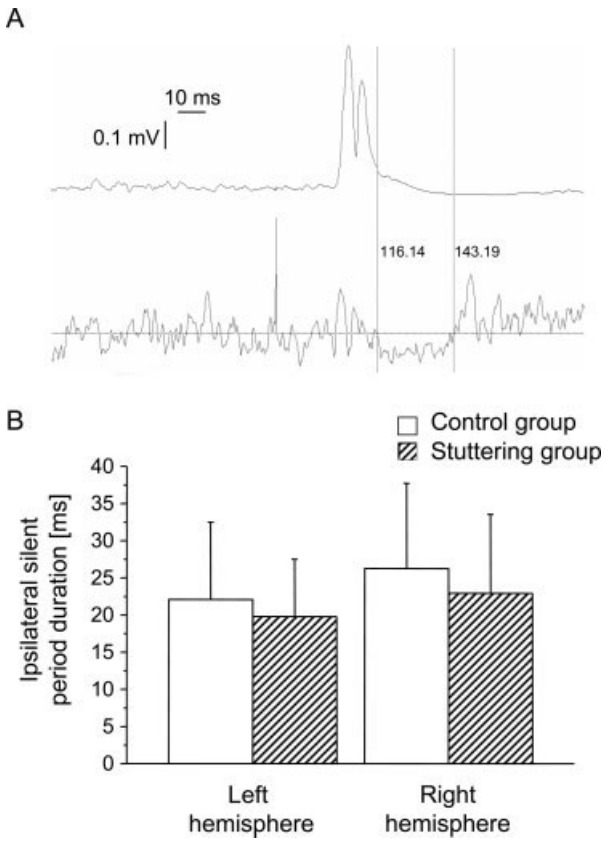

FIG. 2. Ipsilateral silent period. **A**: original recording of contralateral, right ADM (upper trace) and ipsilateral, left ADM recording (lower trace). Rectified and averaged mean of 10 recordings (Signal 2.16 averaging software). Note measurement of ipsilateral silent period duration as a function of pre-TMS baseline EMG activity. ISP duration in this example, 27.1 ms (143.19 ms–116.14 ms). **B**: ipsilateral silent period duration from a transcranial magnetic stimulation paradigm using 1 coil and voluntary muscle activation. All symbols represent the mean ± standard deviation.

SD 6.9% (31.4 SD 7.5) in controls and 35.1 SD 6.8 (35.0 SD 4.9) in the stuttering group.

DISCUSSION

These results for IHI and iSP do not indicate an abnormal interplay between the primary motor cortices of either hemisphere in PDS. This is consistent with a normal intracortical inhibition previously described in patients with PDS.[22] The abnormal right motor and premotor activity observed in imaging studies on PDS are not likely to reflect altered primary motor cortex excitability, but are likely to have a more premotor origin.

The short IHI interstimulus intervals (up to 10 ms) vary from the longer ones (10–50 ms) in that they are not correlated with the iSP[23] and not affected by Gabaergic medication.[24] Other authors have encountered some variability in the results at these short intervals, such as the inconsistent facilitation observed at the interval 2 ms in the original report of Ferbert et al.[13] We also observed traces of such facilitation—insignificant at a group level—at the same interval. In addition, we already found an inhibition at the interval of 5 ms with the test pulse over the left hemisphere and in the control group only. This slightly varies from the findings of Chen,[23] who did not find a significant inhibition at either of these intervals. We are not aware of other authors who have studied the shorter IHI intervals of 5 ms and 6 ms in the same group of subjects.

The trend for an asymmetry of IHI observed at the interval of 6 ms is consistent with earlier findings of Bäumer et al.[25] In right-handed subjects, these authors reported inhibition at this interval with a test pulse over the right hemisphere, but no inhibition with the test pulse over the left hemisphere.

We cannot exclude that studying articulatory muscles might have yielded different results. However, noninvasive surface EMG traces from facial muscles are often contaminated by considerable background noise and may contain additional activity such as ipsilateral potentials from the conditioning pulse, making a reliable assessment of IHI very difficult. In addition, hand muscle representations are closely linked to and reflect the excitability of speech muscle representations, as has been shown in a study of hand muscle MEP facilitation during speech.[26] Finally, adults afflicted with PDS show subtle abnormalities in bimanual coordination,[27] suggesting motor execution abnormalities involving hand representations.

The IHI results obtained with the target muscle at rest cannot exclude eventual abnormalities of IHI under voluntary muscle activation. In addition, studying a larger range of conditioning or test intensities may yield subtle IHI group differences missed here.

In summary, our results make the interplay between the primary motor cortices less likely to play a decisive role in PDS.

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Kathrin Knappmeyer: Project—Organization and Execution; Statistical analysis—Organization; Manuscript—Review and Critique; Evke Jane Hunter: Project—Execution; Statistical Analysis—Organization; Manuscript—Review and Critique; Alexander Wolff von Gudenberg: Project—Organization; Statistical Analysis: Design; Manuscript—Review and Critique; Nicole Neef (maiden name Spindler): Project—Organization and Execution; Statistical Analysis—Execution; Manuscript—Review and Critique; Walter Paulus: Project—Conception; Statistical Analysis—Design; Manuscript—Review and Critique.

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Phenotype Variability in Spinocerebellar Ataxia Type 2: A Longitudinal Family Survey and a Case Featuring an Unusual Benign Course of Disease

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Video 

Abstract: **We report a 67 years old female patient out of a multigenerational family with spinocerebellar ataxia type 2 (SCA2) with an unusually benign course of disease. Although all SCA2 gene carriers have by now developed the predominant gait ataxia and brainstem oculomotor dysfunction, the index patient presented with a very mild course of disease, scoring only six points on the Scale for the Assessment and Rating of Ataxia after a disease duration of 13 years. Otherwise, intragenerational variability within family members such as the age at onset of disease and the course of disease was low. Reinvestigation of the genetic background variables in the SCA2 gene carrier reported here showed 27 repeats in the normal allele and 37 noninterrupted repeats in the abnormal allele. Interestingly, this patient has been taking lithium-carbonate over more than 30 years because of psychotic depression. Although anecdotic, this SCA2 case may provide promising insights into possible disease modifying mechanisms in SCA2.** © 2009 Movement Disorder Society

Key words: spinocerebellar ataxia type 2; phenotype-genotype correlation; cerebellar ataxia

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant cerebellar ataxia (ADCA), which represents about 14% of ADCA pedigrees in the European population.[1,2] SCA2 is characterized by progressive cerebellar ataxia and slow saccadic eye movements. Neuropathologically, SCA2 is characterised by prominent cerebellar and brainstem atrophy. Additional basal ganglia pathology, especially in the substantia nigra may also be present.[3,4] The SCA2 phenotype is caused by a triplet repeat expansion in the 5′ coding region of the Ataxin 2 gene (ATXN2) on chromosome 12. The most common disease causing alleles have 37–39 CAG repeats, whereas normal alleles have 31 or fever CAG repeats.[5] The presence of one abnormal allele is diagnostic for SCA2 and penetrance is 100%.

During this first long-term clinical follow-up of a large multigenerational SCA2 family, we observed one SCA2 gene carrier who did not develop the classical SCA2 phenotype. Because "reduced penetrance" has not been observed in SCA2, so far, this case is of particular interest regarding genetic or environmental factors with potential disease modifying effect.

PATIENTS AND METHODS

Clinical Evaluation

Twenty-one adult SCA2 gene carriers out of three consecutive generations were regularly examined between 1991 and 2008. Using a standard examination procedure, all subjects were personally interviewed and clinically examined at their homes by one of the authors (S.B. or S.H.). Clinical findings such as severity of limb ataxia and dysarthria were rated using the Scale for the Assessment and Rating of Ataxia (SARA).[6] For intergenerational comparison of progression, the following milestones in the disease course were defined: Onset of gait difficulties, loss of independent ambulation, and permanent use of a wheelchair. Besides the severity of ataxia, nonataxia symptoms, co-morbidities, and medication were regularly assessed. Further demographic details are listed in Table 1.

Genetics

The repeat lengths of the expanded and normal alleles were regenotyped in all affected family members. The CAG stretch of ataxin-2 was amplified by PCR.[7]

RESULTS

Family Survey

At the time of the last investigation, the whole SCA2 family consisted of twenty-one affected subjects (5 males, 16 females). By the year of 2008, 6 patients have died (mean age at death 59 years [range 37–76]). In four cases, the cause of death was SCA2, one patient died of cancer and one patient committed suicide.

Additional Supporting Information may be found in the online version of this article.

The authors have nothing to disclose.

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TABLE 1. *Genetic and demographic variables of the sibs and the patient with benign course of SCA2 (ID 1)*

ID	Age/sex	Duration of disease	SARA score	Number of repeats normal/expanded	SNP normal/expanded	CAA normal/expanded	Position CAA
1	67/f	13	6	27/37	CC/GT	3/0	9, 14, 19
2	71/f	20	32	27/37	CC/GT	3/0	9, 14, 19
3	38/f	13	30	22/43	CC/GT	2/0	9, 14
4	46/f	9	12	22/38	CC/CC	1/0	14
5	43/f	5	16	16/38	GT/GT	1/0	8
6	21/m	14	27	22/50	CC/GT	2/0	9, 14

CAG repeat length in affected members of this SCA2 family ranges from 37 to 50 repeats. Although the subjects in the first affected generation had CAG repeat lengths (longer allele) between 37 and 41, these ranges were between 38 and 47 repeats in the second generation. In the third affected generation, CAG repeat length was beyond 50. The shorter repeat length was in the range of 21–27 (mean 22.6) in the first generation and 21–22 (mean 21.7) in the second generation. In the third generation, there were two affected children (50 repeats) in one of whom we were not able to obtain genetic confirmation.

Intergenerational comparison of age at onset revealed anticipation of up to 15 years. Individuals of the first affected generation (n = 9) had disease onset in their mid-forties (mean 43.4 years, range 35–54) and their disease course was slow, allowing them remaining functional until later in life (walking aid: mean 51.7 years; wheelchair bound at the mean age of 58.3 years). The second and third affected generation (n = 10/2) showed onset of disease in their mid-twenties (age at onset: 26 years, range 20–35) or childhood (3 years, 10 years). In the second generation, earlier onset of disease went along with a more rapid course of disease (walking aid: 33.3 years, range 25–45 years; wheelchair: 37.7 years, range 30–48 years), and in the third generation, severe gait and stance problems occurred in childhood.

Case

A 67-year-old woman (out of the first generation) was first seen in 1990 at the age of 49 when genetic testing for SCA2 revealed 37 CAG repeats, clearly identifying her as a SCA2 gene carrier. At her first visit, she was clinically unaffected and has been regularly followed up in 5 year intervals. In 1995, when she was 54 years old, she developed subtle signs of gait ataxia. At last follow-up in 2008, she was mildly ataxic in stance and gait and had reduced saccade velocity (SARA score six points, see video). Additional neurological symptoms, especially extrapyramidal or pyramidal signs were absent. The patient is fully independent in her activities of daily living. Her medical records revealed admission to a psychiatric hospital because of a "psychotic depression" at the age of 35. Since then she has been on uninterrupted treatment with low-dose lithium-carbonate (450 mg per day). Her mother and both of her sisters have genetically confirmed SCA2 (see also pedigree). Onset of disease of her sisters was in the fifth decade (at the age of 54 and 51 years). Both were wheelchair-bound by the end of their sixth decade (68, 70 years). The older and more affected sister (repeat length: 21/39) died at the age of 75. Interestingly, the younger sister has the same repeat lengths as the "index patient" (repeat length: 27/37). She neither differs from the whole cohort regarding onset of disease nor in phenotype. The offspring of the "index patient" and her living sister consists of five persons. The index patient has three children one of whom is moderately affected (onset of disease at the age of 35, repeat length 16/38). Her living sister has two affected children with a disease onset in their mid-end twenties (female: 25 years, repeat length 22/43, male: 30 years, repeat length: 22/39). One male grand-child is severely affected; his age at onset was before the age of ten (for pedigree, see Fig. 1).

Correlation Analysis

Correlation analysis using Pearson's correlation coefficient revealed significantly earlier disease onset in the second and third generation of this SCA2 pedigree ($P = 0.002$, $r = -0.633$) resulting in earlier need of walking aids ($P < 0.0001$, $r = -0.865$) and wheelchair ($P = 0.007$, $r = -0.786$). The shorter allele did not have impact on these milestones of disability in SCA2.

DISCUSSION

The present case of genetically confirmed SCA2 from a large multigenerational family presented with

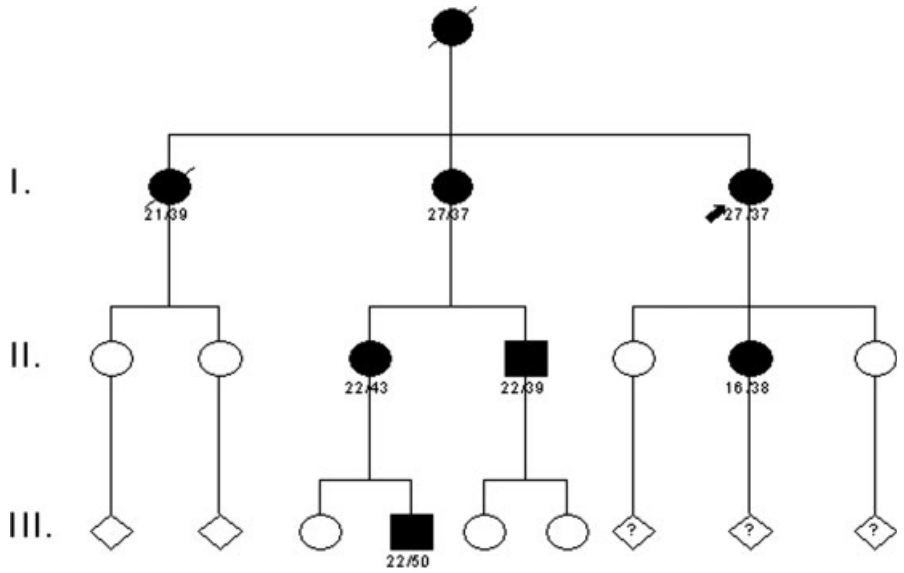

FIG. 1. SCA2 Pedigree. I, II, and III label the different generations; the filled out symbols mark a SCA 2-positive status; the numbers below the affected individuals show the number of repeats (normal/expanded), the index patient is highlighted with an arrow; the two crossed out individuals have died.

unusually benign course of disease which was strikingly attenuated when compared with what was observed in all the other affected members of this pedigree.

Genetic re-evaluation of the whole family revealed an intergenerational increase of the poly-glutamine stretch by four CAG repeats. Anticipation with earlier onset and more rapid course of disease most likely reflects this intergenerational polyglutamine enlargement.[5,8] In line with this, age at onset and clinical milestones occurred significantly earlier in subsequent generations. In the oligosymptomatic case, CAG repeat length in the expanded allele encompasses 37 CAG repeats clearly indicating a disease causing mutation.[1] Repeat expansion in the normal allele was 27, which is considerably longer when compared with the average length of the short allele in SCA2. Thus, in contrast to SCA1 in which an interference of the normal allele's size with disease severity has been reported, there is no evidence for such effect in SCA2.[8,9] Only recently, CAA interruptions have been suggested to interfere with phenotype variability in SCA2.[10] According to findings by Charles and coworkers interrupted CAG repeats in SCA2 are more prone to result in the parkinsonian SCA2 variant, whereas similar sized but uninterrupted repeats were associated with the cerebellar SCA2 phenotype. There were no interrupted abnormal poly-glutamine stretches detectable in the case reported here.

Moreover, epigenetic phenomena such as regulation of gene expression,[8,11,12] life style, and environmental factors[11] have been attributed to interfere with pure mendelian rules of inheritence in SCA2. Because all family members live in the same environment for several generations, environmental causes for phenotype variability in a single case are not likely. There was, however, a history of "psychotic depression" in her mid-thirties when the patient was admitted to a psychiatric unit and put on lithium therapy. Since then the patient has been taking 450 mg lithium-carbonate daily. In humans, chronic lithium intake may potentially be toxic for Purkinje cells and result in irreversible cerebellar dysfunction, especially in case of intoxication.[13] Recent findings in transgenic mouse models, in turn, indicate disease modifying properties of lithium-ions.[14–17]

Although, this case is anecdotic, we feel that in the light of increasing evidence for beneficial actions of lithium-ions in neurodegeneration,[14,18] a long-term use of low dose lithium-carbonate that coincided with a mild SCA2 phenotype may be of interest for future clinical investigations.

LEGEND TO THE VIDEO

The video is showing the examination of the index patient in 2008. It is illustrating the very benign course

of disease by means of the following tasks: Speech, ocular pursuit, metria of the saccades, standing capacities with eyes open, walking capacities, pronation-supination alternating movements, and finger-to-nose test. Because of a recent fracture of the left wrist, the alternating movements on this side are slowed.

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Author Roles: Research project: A. Conception, B. Organization, C. Execution; Statistical Analysis: A. Design, B. Execution, C. Review and Critique; Manuscript: A. Writing of the first draft, B. Review and Critique. S. Hering MD: 1.A+B+C, 2.B+C, 3.A (including examination and documentation of patients), C. Achmüller PhD: 1.B+C, 2.C, 3.B (including laboratory work), A. Köhler MS: 1.B+C, 2.C, 3.B (including laboratory work), W. Poewe MD: 2.C, 3.B, R. Schneider PhD: 1.A, 2.A, 3.A+B (including laboratory work), SM. Boesch MD: 1.A+B+C, 2.B+C, 3.A (including examination and documentation of patients).

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A Novel *KCNA1* Mutation Associated with Global Delay and Persistent Cerebellar Dysfunction

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Abstract: **Episodic Ataxia Type 1 is an autosomal dominant disorder characterized by episodes of ataxia and myokymia. It is associated with mutations in the *KCNA1* voltage-gated potassium channel gene. In the present study, we describe a family with novel clinical features including persistent cerebellar dysfunction, cerebellar atrophy, and cognitive delay. All affected family members have myokymia and epilepsy, but only one individual has episodes of vertigo. Additional features include postural abnormalities, episodic stiffness and weakness. A novel *KCNA1* mutation (c.1222G>T) which replaces a highly conserved valine with leucine at position 408 (p.Val408Leu) was identified in affected family members, and was found to augment the ability of the channel to inactivate. Together, our data suggests that *KCNA1* mutations are associated with a broader clinical phenotype, which may include persistent cerebellar dysfunction and cognitive delay.**

Key words: *KCNA1*; EA1; cerebellar atrophy; cognitive dysfunction

Episodic Ataxia type 1 (EA1) is a rare autosomal dominant disorder associated with *KCNA1* mutations that presents in childhood with brief episodes of ataxia and continuous myokymia.[1,2] The clinical spectrum of EA1 has expanded to include epilepsy, episodes of muscle stiffness, postural abnormalities and weakness.[2–8] Persistent cerebellar dysfunction with cerebellar atrophy is typically absent in patients with EA1[9] but is a characteristic feature of Episodic Ataxia Type 2 (EA2), which is associated with mutations in the P/Q-type voltage-gated calcium channel gene *CACLNA4*.[10,11]

We describe and present functional studies of a novel *KCNA1* mutation in a family with EA1 in whom there are clinical features not previously described, including persistent cerebellar dysfunction, cerebellar atrophy and delayed cognitive development.

PATIENTS AND METHODS

Subjects

The proband (Patient III-1) (see Fig. 1A,B) is a 4 yr 9-mo old boy with seizures, global developmental delay, myokymia with postural abnormalities, and episodes of muscle stiffness triggered by illnesses. The seizures started in infancy and are controlled on carbamazepine. He walked at 3 yr and his first word was at 4 yr. At 4 yr 9 mo, he functions at a cognitive level of 24 mo. His receptive and expressive language skills are at a 14-mo level and his motor skills are at an 18 mo level. He has chronic swallowing difficulties and gastroesophageal reflux disease requiring a G-tube. Examination in infancy revealed postural abnormalities. Current examination reveals increased tone, myokymia and mild gait ataxia. Head MRI was normal at 4 mo. Electroencephalograms (EEGs) were normal or demonstrated bilateral epileptiform activity.

Patient III-2 (Fig. 1A) is a 14-mo old boy with seizures, myokymia and mild global developmental delay. Seizures began at 3 wk and are controlled on carbamazepine. His examination revealed periocular myokymia and increased tone. EEGs were normal or demonstrated rhythmic spikes in the right temporal region.

Patient II-1 (Fig. 1A,C) is a 29-yr old woman with mild cognitive difficulties, episodic vertigo, myokymia, and persistent cerebellar dysfunction. She has had infrequent episodes of muscle stiffness triggered by heat. She describes mild generalized weakness exacerbated by temperature extremes, and difficulty swallowing cold substances. Episodes of vertigo, triggered by activity and heat, began at 2 yr. Seizures began in the neonatal period and were controlled on phenytoin which was discontinued at 4 yr. Persistent dysarthria and ataxia was first recognized at 3 yr. She received learning assistance, was placed in a practical skills class and did not formally graduate. A recent

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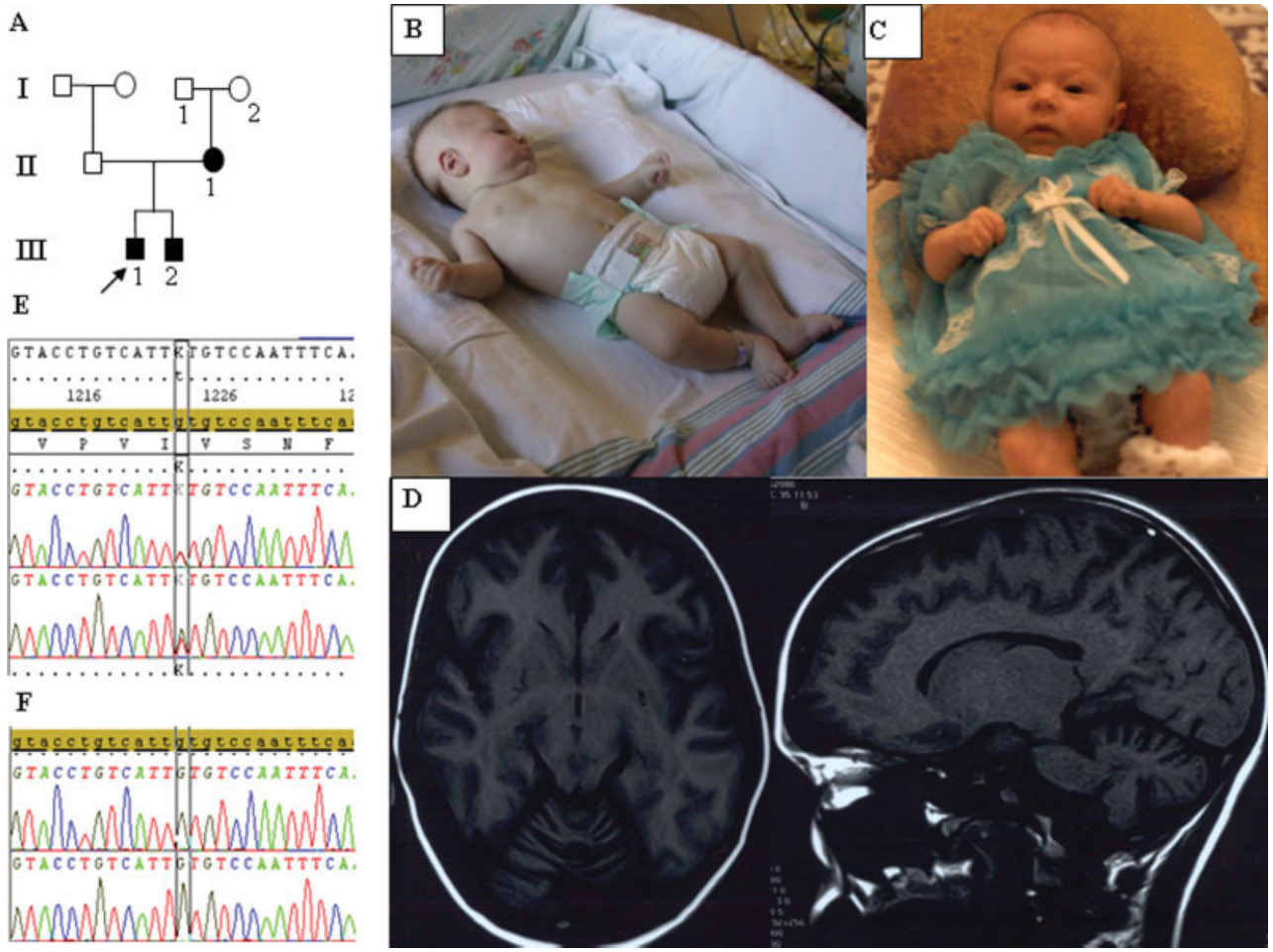

FIG. 1. Pedigree and clinical features. (**A**) Pedigree of family. Blackened symbols represent affected individuals. DNA available from numbered individuals. (**B**) Patient III-1 at 4 mo with tightly clenched fists and persistent flexion of hips and knees. (**C**) Patient II-1 at 2 mo: tightly clenched fists. (**D**) Patient II-1 head MRI at age 17 yr demonstrating cerebellar atrophy. (**E**) Sequencing of *KCNA1* revealed heterozygosity for a nucleotide transversion (G>T) in affected family members (III-1, III-2, and II-1), (**F**) but not in the unaffected family members (I-1, I-2) or normal control. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

examination revealed dysarthric speech, mild facial weakness and myokymia of facial muscles and hands. There was also bilateral calf hypertrophy and mild generalized weakness. An intention tremor; difficulty with fine finger and rapid alternating movements; and ataxic gait were also present. Electromyography (EMG) studies demonstrated myokymic discharges, and after muscle cooling to 20°C there was electrical silence following dense fibrillation potentials. With this, she was unable to abduct her fingers. No myotonic discharges were present. A head CT scan at 4 mo was normal. A head MRI at 17 yr revealed mild generalized atrophy of cerebellar hemispheres (Fig. 1D), which was unchanged on repeat scan at age 27 yr.

Genetic and Functional Studies

DNA was extracted from relevant family members (GentraSystems, Minneapolis, MN). PCR amplification and direct sequencing of the coding and flanking regions of *KCNA1* was performed.[12] SeqScape software (Applied Biosystems, Foster City, CA) was used for comparative analysis of resulting sequence to *KCNA1* consensus sequence (NM_000217). Genotyping of familial samples was performed using AmpfISTR Identifiler chemistry (Applied Biosystems, Foster City, CA) to verify identity and stated relationships.

As described previously, Chinese hamster ovary-K1 (CHO) cells (ATCC, Manassas, VA), were transiently co-transfected with pcDNA3.1 vectors encoding wildtype or mutant KCNA1 channels and green fluorescent pro-

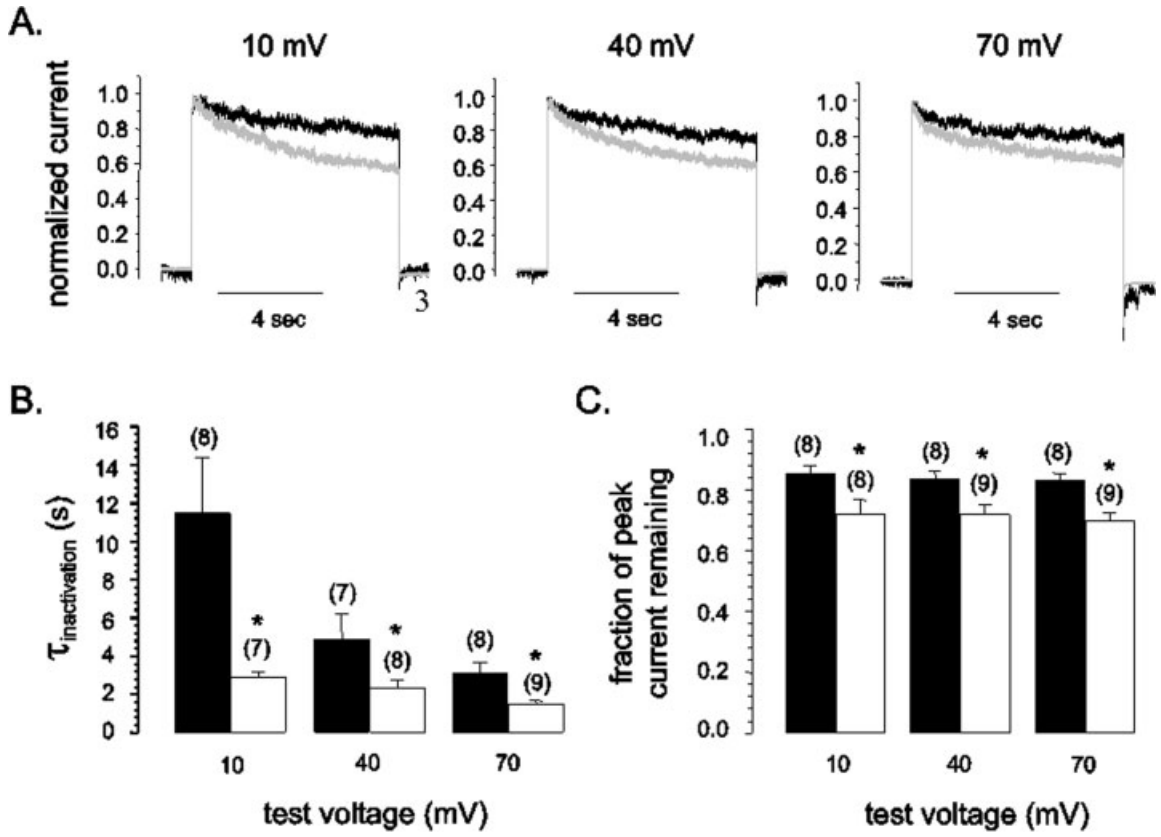

FIG. 2. Inactivation of the human KCNA1 channel is enhanced by the V408L mutation. (**A**) Representative current traces from CHO cells transfected with wildtype (black line) and mutant (gray line) channels elicited by 8 voltage pulses to +10 mV, +40 mV, and +70 mV from a holding potential of −80 mV. Traces are normalized to their maximum (peak) values. (**B**) Plot of time constants of inactivation (τ) determined from a single exponential fitting procedure of current traces obtained from cells expressing the wildtype (filled bars) or mutant (unfilled bars) channels at the three test potentials shown in A. τ values were significantly faster for the mutant compared with wildtype channels (*t*-test, $P < 0.05$). The numbers in parentheses represent the number of cells used for each condition and the asterisk above the numbers signifies a significant difference (*t*-test, $P < 0.05$). (**C**) Plot of the fraction of peak current remaining after 8 sec for the wildtype (filled bars) and mutant (unfilled bars) channels at the three test potentials. The fraction of peak current remaining after 8 sec was significantly less for mutant compared with wildtype channels. For either the wildtype or mutant channel, the fraction of current remaining after 8 sec was the same at each test potential. The numbers in parentheses represent the number of cells used for each condition and the asterisk above the numbers signifies a significant difference (*t*-test, $P < 0.05$). Data are reported as mean ± S.E.M. Experiments were conducted at room temperature (20–22°C). Series resistance was not compensated and currents were not leak-subtracted.

tein.[13] After the appearance of green fluorescence (24–48 hr later), cells were transferred to a recording chamber (~200-μL volume) and continually perfused (0.5–1.0 mL/min) with an extracellular solution (5.4° mM KCl, 135° mM NaCl, 0.5° mM $MgCl_2$, 1.9° mM $CaCl_2$, 5° mM HEPES, adjusted to pH 7.4° with NaOH). Pipettes were filled with a solution of 130° mM potassium aspartate, 10° mM NaCl, 0.5° mM $MgCl_2$, 5° mM HEPES, and 1° mM EGTA and adjusted to pH 7.4° with KOH. Currents were measured using borosilicate glass electrodes, which had a resistance of 2.0–4.0 mohms when filled, and recorded using an Axopatch 200B amplifier and Clampex software (Axon Instruments). Data were filtered at 2° kHz and analyzed using Clampfit (Axon Instruments) and Origin (Microcal) software.

RESULTS

Sequencing of *KCNA1* revealed heterozygosity for a nucleotide transversion (G>T) in all affected family members, but not in unaffected grandparents or normal control (see Fig. 1E,F). This transversion results in the substitution of leucine (L) for valine (V) at amino acid position 408, a highly conserved residue located in the distal pore region of the KCNA1 channel, which was previously implicated in episodic ataxia when con-

verted to alanine (A).[1] Genotyping confirmed identity and stated relationships indicating that the V408L mutation arose *de novo* in patient II-1 and was transmitted to her offspring (III-1 and III-2).

Because a mutation of valine 408 to alanine was previously found to enhance KCNA1 channel inactivation,[14] this behavior was analyzed in CHO cells transfected with either wildtype or mutant (V408L) human KCNA1 channels (see Fig. 2). Both the rate and extent of inactivation were greater in the mutant channel compared with the wildtype channel. Neither the voltage range over which channel opening occurred nor current amplitude was significantly altered by the mutation (data not shown).

DISCUSSION

We report a family whose clinical features further expand the wide clinical spectrum of EA1. The proband's mother (II-1) has persistent cerebellar dysfunction associated with cerebellar atrophy on neuroimaging. The proband (III-1) also has mild gait ataxia. Past reports of patients with EA1 have described mild cerebellar dysfunction in some affected family members. Findings included intention tremor and mild difficulties with tandem gait and/or arm coordination.[3,15,16] In contrast to these earlier reports, the cerebellar dysfunction in the proband's mother (II-1) appears to be more severe with an earlier onset and greater functional impact. Her head MRI also demonstrated cerebellar atrophy, a feature which has not been reported previously in EA1. It is possible that treatment in infancy with phenytoin may have contributed to the severity of the cerebellar dysfunction and atrophy present in our patient. Given the reports indicating that phenytoin treatment may be associated with permanent cerebellar dysfunction and atrophy,[17,18] this case suggests that phenytoin should be used with caution in young children with EA1.

This family demonstrates that cognitive dysfunction may also be a feature of EA1. The mother (II-1) has learning difficulties and was educated in a life skills program. In addition, the proband has marked global delay with severe receptive and expressive language delay. Patient III-2 is also globally delayed. We are aware of only one other report of cognitive dysfunction described as mild-to- moderate learning difficulties in one individual with EA1.[4]

Exposure to warm temperature is recognized as a potential provoking factor for symptoms of EA1.[5,7] In our family, the proband's mothers' symptoms and EMG results were exacerbated by cold temperatures, suggesting that symptoms of EA1 are provoked by temperature extremes. Sensitivity to cold temperatures is not well recognized for EA1; however, mild cramping and worsening of myokymia with cold exposure has been described in two individuals with EA1.[2,16] Mice lacking KCNA1 also demonstrated cooling-induced hyperexcitability in synaptic transmission.[19] Therefore, KCNA1 may inhibit involuntary muscle contractions during decreases and increases in external temperature by stabilization of central synaptic transmission.

The mutation identified in this family is located at the same position as a previously reported mutation (V408A) causing EA1 in an unrelated family.[1] Like the V408A mutation, V408L causes the channel to inactivate faster than the wildtype channel.[14] This would be expected to reduce the contribution of KCNA1 channels to repolarization of the membrane potentially after neuronal firing resulting in the increased excitability of neurons.

A correlation between the degree of KCNA1 dysfunction and EA1 phenotype has been suggested. Mutations associated with relatively severe disease, poorly responsive to medications or associated with seizures, tend to show profound reductions in KCNA1 current amplitude, whereas milder or typical EA1 cases are associated with mutations altering voltage channel activation which more subtly alters potassium flow.[20] The more severe phenotype found here suggests that the altered KCNA1 inactivation more profoundly disrupts potassium flow. However, the V408A mutation found previously, which augments channel inactivation in the same way as V408L, is associated with a much less severe phenotype[1,9,14] than that found in this study, suggesting that other factors must contribute to the disease. The determination of these contributing factors and more strongly linking genotype to phenotype may help to develop gene and mutation specific therapies for patients with EA1.

In conclusion, patients with *KCNA1* mutations may also develop persistent cerebellar dysfunction, have cognitive impairment, and exacerbation of symptoms on exposure to cold temperatures. Functional studies demonstrate channel dysfunction but do not fully explain the interfamilial or intrafamilial phenotypic variability of Episodic Ataxia Type 1.

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