J Neurol (2001) 248 : 311–314

ORIGINAL COMMUNICATION

Michael Abele
Katrin Bürk
Franco Laccone
Johannes Dichgans
Thomas Klockgether

Restless legs syndrome in spinocerebellar ataxia types 1, 2, and 3

Received: 18 July 2000
Received in revised form:
10 November 2000
Accepted: 15 November 2000

M. Abele (✉) · K. Bürk · J. Dichgans
Department of Neurology
University of Tübingen
Hoppe-Seyler-Strasse 3
72076 Tübingen, Germany
e-mail: michael.abele@uni-bonn.de
Tel.: +49-228-2875735
Fax: +49-228-2875024

M. Abele · T. Klockgether
Department of Neurology
University of Bonn
Sigmund-Freud-Strasse 25
53105 Bonn, Germany

F. Laccone
Department of Human Genetics
University of Göttingen, Germany

Abstract To identify the prevalence and determinants of restless legs syndrome (RLS) in spinocerebellar ataxia (SCA) we studied 58 patients with a molecular diagnosis of SCA1, SCA2 and SCA3. Data on the symptoms of RLS were collected by a standardized questionnaire, and RLS was diagnosed when patients met the four minimal criteria of the syndrome as recently defined by an international study group. In addition, we studied the relationship between RLS and age, age at ataxia onset, CAG repeat length, and nerve conduction and evoked potentials data. RLS was significantly more frequent in SCA patients than in controls (28 % vs. 10 %). Age at RLS onset in SCA was 49.0 ± 10.9 years. There were no significant differences in nerve conduction or evoked potentials between RLS and non-RLS SCA patients. The probability of developing RLS increased with age but not with CAG repeat length or higher age of ataxia onset. The data provide evidence that patients with SCA1, SCA2 and SCA3 are per se more susceptible to RLS than non-affected individuals. The probability of developing RLS is related principally to the period over which the CAG repeat mutation exerts its effect and not to CAG repeat length or age of ataxia onset.

Key words Autosomal dominant cerebellar ataxia · Restless legs syndrome

Introduction

RLS is clinically characterized by an urge to move the limbs, often associated with paraesthesia and dysaesthesia that are worse at rest and at least temporarily relieved by activity. Symptoms are usually more severe in the evening. It was formerly believed that RLS is due to peripheral neuropathy [3, 5], but more recent studies suggest that it has a central origin in many cases [2, 21, 26, 27, 30]. RLS may be either idiopathic or symptomatic due to iron deficiency, uraemia, pregnancy, and familial amyloidotic polyneuropathy [22, 29]. RLS is associated with periodic limb movements during sleep (PLMS) in up to 90 % of the patients [10, 15–17]. In many patients RLS/PLMS causes severe disturbance of sleep as well as excessive daytime sleepiness (EDS). Frequent complaints of patients with spinocerebellar ataxia (SCA) concerning limb paraesthesias and motor restlessness led us to study the prevalence of RLS in SCA1, SCA2 and SCA3. These are the most common mutations causing dominant ataxias in Germany. All three mutations are characterized by ataxia due to cerebellar degeneration with variable involvement of other parts of the central nervous system and peripheral axonal neuropathy. In each of the disorders the mutation is an unstable, expanded CAG repeat present within the coding region of a gene of unknown physiological function.

Patients and methods

Patients and controls

A standardized questionnaire was sent to 75 unselected patients with a molecular diagnosis of SCA1, SCA2 or SCA3. The study was performed in the 58 patients who responded to the questionnaire (13 SCA1, 22 SCA2 and 23 SCA3 patients). All patients gave informed consent to participate in the study. The molecular diagnosis of SCA1, SCA2 and SCA3 was established using standard laboratory procedures [11, 12, 19]. All patients had been personally interviewed and examined during the past 2 years in our ataxia clinic by M. A. or K. B.. The control group consisted of 40 age- and sex-matched patients who were seen consecutively in our out-patient clinic for lower back pain, headache or dizziness. None of them had any clinical signs of polyneuropathy or central nervous system disorders.

The questionnaire included questions related to minimal criteria for RLS as recently defined by an international study group [28]: (a) Desire to move the limbs usually associated with paraesthesia/dysaesthesia; (b) motor restlessness; (c) symptoms are worse or exclusively present at rest (i. e. lying, sitting) with at least partial and temporary relief by activity, and (d) symptoms are worse in evening/night. In addition, we asked the age at onset of the respective symptoms. RLS was diagnosed only when patients met all four minimal criteria.

Electrophysiological studies

Electrophysiological data were available for 8 SCA1, 11 SCA2 and 18 SCA3 patients. These included nerve conduction studies, somatosensory evoked potentials, brainstem auditory evoked potentials and motor evoked potentials following transcranial magnetic stimulation. The electrophysiological data were obtained using standard laboratory procedures [1].

For all evoked potentials latencies beyond the threshold of 3 SD of the mean of normative data from our laboratory and non-evoked potentials were considered abnormal.

Statistical analysis

Statistical analysis was performed using the χ^2 test (frequency of abnormal results), linear and logistic regression or analysis of variance followed by Tukey's test (quantitative data). To select the appropriate statistical model for multiple significant regressors, we used a stepwise regression procedure based on the Akaike information criterion for continuous data and a logistic regression model for multiple regressors for nominal data.

Results

Frequency of RLS in SCA mutations

RLS was present in 3 of the 13 SCA1 (23 %), 6 of the 22 SCA2 (27 %) and 7 of the 23 SCA3 patients (30 %). Mean age of RLS patients was 57.9 ± 10.5 years. Mean age of RLS onset was 49.0 ± 10.9 years (SCA1, 47.7 ± 3.8 years; SCA2, 44.3 ± 8.4 years; SCA3, 53.6 ± 13.7 years). Latency of RLS onset with respect to ataxia onset was 8.3 ± 7.2 years in SCA1, –3.8 ± 19.3 years in SCA2 and 6.6 ± 5.9 years in SCA3. There were no significant differences between the SCA groups (Table 1). Mean age of the control group was 48.9 ± 14.3 years. RLS was present in 4 of 40 controls (10 % vs. 28 % in all SCA patients; $P < 0.05$) with a mean age of RLS onset of 46.5 ± 23.1 years.

Determinants of RLS in SCA

SCA patients with RLS were significantly older (57.9 ± 10.5 years vs. 45.8 ± 12.8 years; $P < 0.01$) and had a later age of ataxia onset (46.0 ± 12.4 years vs. 35.8 ± 11.7 years; $P < 0.01$) than SCA patients without RLS. Simple logistic regression revealed significantly increased probability to develop RLS with higher age of ataxia onset ($P < 0.01$) and higher age ($P < 0.01$). To further analyse the relationship between RLS, age at ataxia onset and age we used a nominal logistic regression model for multiple regressors. This analysis showed that age was the only significant covariable ($P < 0.01$). The addition of any other covariable did not yield a better model fit.

To study whether CAG repeat length has an additional effect on the development of RLS we performed separate analyses of SCA1, SCA2 and SCA3. In SCA1 there was no significant effect of age, age at ataxia onset or CAG repeat length on probability of RLS, or age at RLS onset. In SCA2 the probability of RLS increased with a later age at ataxia onset ($P < 0.05$), higher age ($P < 0.01$) and fewer CAG repeats ($P < 0.05$). A nominal logistic regression model for multiple regressors failed to show a predominant effective covariable; there was no effect of age of ataxia onset and CAG repeat length on age of RLS onset. In SCA3 age at RLS onset was positively correlated with age at ataxia onset ($P < 0.01$) and nega-

Tab. 1 Characteristics of 58 SCA patients and 40 controls

	Controls (*n*=40)	SCA1 (*n*=13)	SCA2 (*n*=22)	SCA3 (*n*=23)
Age	48.9 ± 14.3	46.3 ± 9.6	47.5 ± 14.5	52.3 ± 13.8
Male/female	18/22	7/6	10/12	10/13
Range of CAG repeats	–	42–52	36–45	63–80
Age of ataxia onset (years)	–	34.1 ± 9.3	36.9 ± 13.4	41.4 ± 13.5
Disease duration (years)	–	9.2 ± 5.8	10.6 ± 7.1	10.7 ± 4.8
Frequency of RLS (%)	10	23	27	30
Age of RLS onset (years)	46.5 ± 23.1	47.7 ± 3.8	44.3 ± 8.4	53.6 ± 13.7
Latency of RLS onset (years)	–	8.3 ± 7.2	–3.8 ± 19.3	6.6 ± 5.9

Tab. 2 Nerve conduction and evoked potential results in SCA1–SCA3 (*MNCV* motor nerve conduction velocity, *CMAP* compound muscle action potential, *SNCV* sensory nerve conduction velocity, *SNAP* sensory nerve action potential, *MEP* motor evoked potential, *SEP* somatosensory evoked potential, *VEP* visual evoked potential, *BAEP* brainstem auditory evoked potential, *% abn* percentage of abnormal results)

	SCA without RLS (*n*=25–29)	SCA with RLS (*n*=7 or 8)	SCA all (*n*=32–37)
MNCV (m/s)	43.6 ± 4.6	43.1 ± 4.7	43.5 ± 4.6
CMAP (mV)	19.4 ± 9.1	16.6 ± 6.9	18.8 ± 8.7
SNCV (m/s)	42.8 ± 6.5	46.9 ± 4.7	43.6 ± 6.3
SNAP (μV)	6.4 ± 5.2	7.0 ± 4.0	6.5 ± 4.9
MEP (% abn)	44	38	42
SEP (% abn)	80	88	82
VEP (% abn)	44	29	41
BAEP (% abn)	42	71	48

tively correlated with CAG repeat length ($P < 0.05$). A stepwise regression procedure based on the Akaike information criterion showed age of ataxia onset as the most effective covariable. The probability of RLS was increased with higher age ($P < 0.05$) and fewer CAG repeats ($P < 0.05$). Again, a nominal logistic regression model for multiple regressors failed to show an independently significant covariable.

Correlation with electrophysiological results

The nerve conduction and evoked potential data are presented in Table 2. There were no significant differences between RLS and non-RLS patients in nerve conduction or multimodal evoked potentials data. In addition, we found no correlation between these data and age at RLS onset or RLS duration.

Discussion

The principal and novel finding of this study is that RLS is significantly more frequent in patients with SCA1, SCA2 or SCA3 than in the general population. RLS was present in 28 % of our SCA1, SCA2 and SCA3 patients but in only 10 % of the control group. The frequency of RLS in the control group corresponds well to the estimated prevalence of RLS of 5–15 % in the general population [7, 14]. The presence of the four minimal criteria of the international RLS study group is considered sufficient for the diagnosis of RLS. However, clinical diagnosis may be complicated by the presence of peripheral neuropathy which is common in SCA1–SCA3 [1]. Future studies in SCA patients should therefore include polysomnographic recordings to confirm the clinical diagnosis of RLS.

Schöls et al. [24] recently reported similar frequencies of RLS in SCA3 (19 of 51 patients who met all four minimal criteria, 37 %), but not in SCA1 (0 of 6 patients) and SCA2 (1 of 11 patients, 9 %) [24]. This discrepancy is most probably due to the smaller number of SCA1 and SCA2 patients in their study.

Our data show an increased probability to develop RLS with higher age. Initial analysis with simple logistic regression suggested an increased probability of RLS with higher age of ataxia onset. Since the age of ataxia onset is inversely correlated with CAG repeat length in SCA1, SCA2 and SCA3 [12, 19, 23], this finding suggests an effect of the CAG repeat length on the probability of RLS. However, subsequent analysis using multivariate methods revealed that this association is an artefact explained by the colinearity between the variables age and age at ataxia onset. The probability of developing RLS is related mainly to age, i. e. the time period over which the CAG repeat mutation exerts its effect, and not to the length of the CAG repeat.

The electrophysiological data show that frequency and severity of neuropathy did not differ between SCA patients with and those without RLS. This observation supports the view that RLS is of central rather than of peripheral origin [2, 21, 26, 27, 30]. However, there was likewise no correlation of RLS with electrophysiological abnormalities in pyramidal and central auditory or somatosensory pathways.

Recent positron-emission tomography studies in idiopathic RLS revealed a mildly decreased dopamine D_2 receptor binding and ^{18}F-labelled dopa uptake in the caudate and the putamen suggesting central dopaminergic dysfunction [21, 27]. Central dopaminergic dysfunction is one potential mechanism causing RLS in SCA patients because degeneration of the striatum or the substantia nigra has been shown to a variable degree in all three SCA mutations [4, 6, 8, 9, 13, 18, 20, 25].

The observation that many SCA patients suffer from RLS is of clinical importance since, in our experience, the RLS symptoms in SCA respond well to levodopa treatment. It is therefore important to specifically ask patients for a history of limb paraesthesia, motor restlessness and sleep complaints in the evaluation of SCA.

References

1. Abele M, Burk K, Andres F, et al (1997) Autosomal dominant cerebellar ataxia type I. Nerve conduction and evoked potential studies in families with SCA1, SCA2 and SCA3. Brain 120:2141–2148
2. Bucher SF, Seelos KC, Oertel WH, et al (1997) Cerebral generators involved in the pathogenesis of the restless legs syndrome. Ann Neurol 41:639–645
3. Callaghan N (1966) Restless legs syndrome in uremic neuropathy. Neurology 16:359–361
4. Durr A, Stevanin G, Cancel G, et al (1996) Spinocerebellar ataxia 3 and Machado-Joseph disease: clinical, molecular, and neuropathological features. Ann Neurol 39:490–499
5. Ekbom KA (1944) Asthenia crurum paresthetica (irritable legs). Acta Med Scand 118:197–209
6. Genis D, Matilla T, Volpini V, et al (1995) Clinical, neuropathologic, and genetic studies of a large spinocerebellar ataxia type 1 (SCA1) kindred (CAG) n expansion and early premonitory signs and symptoms. Neurology 45:24–30
7. Gibb WR, Lees AJ (1986) The restless legs syndrome. Postgrad Med J 62:329–333
8. Gilman S, Sima AA, Junck L, et al (1996) Spinocerebellar ataxia type 1 with multiple system degeneration and glial cytoplasmic inclusions. Ann Neurol 39:241–255
9. Goldfarb LG, Chumakov MP, Petrov PA, et al (1989) Olivopontocerebellar atrophy in a large Iakut kinship in eastern Siberia. Neurology 39:1527–1530
10. Hening WA, Walters A, Kavey N, et al (1986) Dyskinesias while awake and periodic movements in sleep in restless legs syndrome: treatment with opioids. Neurology 36:1363–1366
11. Imbert G, Saudou F, Yvert G, et al (1996) Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats. Nat Genet 14:285–291
12. Kawaguchi Y, Okamoto T, Taniwaki M, et al (1994) CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat Genet 8:221–228
13. Kish SJ, Guttman M, Robitaille Y, et al (1997) Striatal dopamine nerve terminal markers but not nigral cellularity are reduced in spinocerebellar ataxia type 1. Neurology 48:1109–1111
14. Lavigne GJ, Montplaisir JY (1995) Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 739–743
15. Lugaresi E, Cirignotta F, Coccagna G, et al (1986) Nocturnal myoclonus and restless legs syndrome. Adv Neurol 43:295–307
16. Montplaisir J, Godbout R, Boghen D, et al (1985) Familial restless legs with periodic movements in sleep: electrophysiologic, biochemical, and pharmacologic study. Neurology 35:130–134
17. Montplaisir J, Boucher S, Poirier G, et al (1997) Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 12:61–65
18. Orozco G, Estrada R, Perry TL, et al (1989) Dominantly inherited olivopontocerebellar atrophy from eastern Cuba. Clinical, neuropathological, and biochemical findings. J Neurol Sci 93:37–50
19. Orr HT, Chung MY, Banfi S, et al (1993) Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat Genet 4:221–226
20. Rosenberg RN, Nyhan WL, Bay C, et al (1976) Autosomal dominant striatonigral degeneration. A clinical, pathologic, and biochemical study of a new genetic disorder. Neurology 26:703–714
21. Ruottinen HM, Partinen M, Hublin C, et al (2000) An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. Neurology 54:502–504
22. Salvi F, Montagna P, Plasmati R, et al (1990) Restless legs syndrome and nocturnal myoclonus: initial clinical manifestation of familial amyloid polyneuropathy. J Neurol Neurosurg Psychiatry 53:522–525
23. Schols L, Amoiridis G, Buttner T, et al (1997) Autosomal dominant cerebellar ataxia: phenotypic differences in genetically defined subtypes? Ann Neurol 42:924–932
24. Schols L, Haan J, Riess O, et al (1998) Sleep disturbance in spinocerebellar ataxias: is the SCA3 mutation a cause of restless legs syndrome? Neurology 51:1603–1607
25. Takiyama Y, Oyanagi S, Kawashima S, et al (1994) A clinical and pathologic study of a large Japanese family with Machado-Joseph disease tightly linked to the DNA markers on chromosome 14q. Neurology 44:1302–1308
26. Trenkwalder C, Bucher SF, Oertel WH, et al (1993) Bereitschaftspotential in idiopathic and symptomatic restless legs syndrome. Electroencephalogr Clin Neurophysiol 89:95–103
27. Turjanski N, Lees AJ, Brooks DJ (1999) Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology 52:932–937
28. Walters AS (1995) Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 10:634–642
29. Walters AS, Picchietti D, Hening W, et al (1990) Variable expressivity in familial restless legs syndrome. Arch Neurol 47:1219–1220
30. Walters AS, Trenkwalder C, Hening WA, et al (1995) Flourodeoxyglucose PET scanning in 5 patients with restless legs syndrome. J Sleep Res 24:365