H Sungurtekin
Aneastesiology and Reanimation Department, Pamukkale University

T Sahiner
Neurology Department, Pamukkale University

H Atalay
Aneastesiology and Reanimation Department, Pamukkale University

S Gur
Neurology Department, Pamukkale University

Correspondence to: Dr E Teke, Pamukkale University, Medicine Faculty, Neurology Department, 20100 Denizli, Turkey; eylemteke@yahoo.com

doi: 10.1136/jnnp.2003.022830

References

1 **Singh S**, Sharma N. Neurological syndromes following organophosphate poisoning. *Neurol India* 2000;**48**:308–13.
2 **Sahin HA**, Sahin I, Arabaci F. Sociodemographic factors in organophosphate poisonings: a prospective study. *Hum Exp Toxicol* 2003;**22**:349–53.
3 **Peter JV**, Cherian AM. Organic insecticides. *Anaesth Intensive Care* 2000;**28**:11–21.
4 **Karalliedde L**, Senanayake N. Acute organophosphorus insecticide poisoning in Sri Lanka. *Forensic Sci Int* 1988;**36**:97–100.
5 **Hollis GJ**. Organophosphate poisoning versus brainstem stroke. *Med J Aust* 1999;**170**:596–7.
6 **Yilmazlar A**, Ozyurt G. Brain involvement in organophoshate poisoning. *Environ Res* 1997;**74**:104–9.
7 **Wang AG**, Liu RS, Liu JH, *et al*. Positron emission tomography scan in cortical visual loss in patients with organophosphate intoxication. *Ophthalmology* 1999;**106**:1287–91.

Coincidence of a large SCA12 repeat allele with a case of Creutzfeld-Jacob disease

The spinocerebellar ataxias (SCAs) are a group of autosomal dominant inherited neurodegenerative disorders characterised by progressive cerebellar dysfunction. Besides cerebellar manifestations a variety of associated neurological signs, such as ophthalmoplegia, dementia, or pyramidal and extrapyramidal signs may occur. At least 21 loci for SCAs including 11 different genes have been identified. SCA 1, 2, 3, 6, 7, and 17 are caused by expansion of a translated CAG repeat in the corresponding gene leading to an expanded polyglutamine tract in the translated protein. In contrast, Holmes and colleagues[1] recently described a large pedigree with a new form of autosomal dominant ataxia (SCA12) associated with an expanded CAG tract in the 5′ untranslated region of the gene PPP2R2B, encoding a brain specific regulatory subunit of protein phosphatase PP2A. Clinical findings in SCA12 patients include upper extremity tremor, cerebellar signs and late onset dementia.[2]

We report on a patient with Creutzfeld-Jakob disease (CJD) carrying a 49 CAG repeat at the SCA12 locus. Additionally, we analysed a large sample of sporadic and hereditary ataxia patients for SCA12 mutations.

A 57 year old man of German origin presented subacutely with gait ataxia and a striking action tremor. Shortly after disease onset, his wife also noticed dysarthria. There was no evidence for neurological diseases in his family. His father died at 43 years from cardiac infarction, his 80 year old mother has no other children. On neurological examination, he showed no signs of cognitive impairment, oculomotor performance was normal. Deep tendon reflexes were depressed, there were no paresis, no pathological signs, and sensory testing was normal for pain, temperature, and touch. His gait was severely ataxic, there was a moderate dysmetria of the upper and lower limbs with a prominent action tremor.

An initial brain MRI was normal. Extensive blood tests including vitamins B12 and E, paraneoplastic antibodies and serum ceruloplasmin showed no pathological results. His cerebrospinal fluid was normal, except for a moderately raised protein level.

Electrophysiology showed subclinical sensory motor neuropathy. A genetic analysis of SCAs revealed a repeat expansion of 49 CAGs in the PPP2R2B gene for SCA12.

The disease rapidly progressed and after four months the patient additionally developed dementia with disorientation and paranoid hallucinations together with a deterioration of his neurological status especially for the ability to coordinate his movements. A second MRI scan now showed bilateral signal hyperintensity in the putamen and caudate nucleus, as well as the frontal, parietal, and insular cortices. EEG showed slowing of background activity with bursts of generalised θ rhythm. Additionally, CSF was positive for 14.3.3 protein leading to the assumption of a probable CJD case.

The patient died two months later because of aspiration pneumonia. Necropsy revealed a brain of 1265 g, which appeared to be unaffected macroscopically. Histological investigations showed moderate to severe spongiform changes with confluent vacuoles, a mild to moderate astrocytic gliosis, and a moderate nerve cell loss in the cerebral neocortex and, to a variable extent, in the basal ganglia, thalamic nuclei, and midbrain structures. The hippocampal formation and brain stem nuclei were comparatively free of pathological changes. Spongiform changes were seen also in the molecular layer of the cerebellum together with a granule cell loss. Kuru plaques could be detected next to Purkinje cells as a hallmark of this special subtype of CJD.[3] With a monoclonal antibody against prion protein (Gö138), perivacuolar prion protein deposits were detectable in cortical areas and plaque-like or granular deposits in the cerebellum. Genetic analysis of the PRNP gene revealed the MV genotype at codon 129.

Additionally, we screened 1028 patients from northern Germany with cerebellar ataxia, including 113 patients with positive family history, and 150 healthy controls for SCA12 mutation.

Repeat expansions in all other known SCA genes had been previously excluded.

SCA12 expansions larger than 50 repeats were not detected in any of the patients or controls. In addition to the CJD patient with 49 CAG repeats, alleles of 40 respectively 41 repeats were found in two patients with late onset sporadic ataxia. All other allele sizes ranged from 4 to 28 CAG repeats with a heterozygosity of 60.7% as shown in table 1. The most common allele containing 10 CAG repeats was found in 61.7% of all chromosomes.

Comment

SCA12 is a very rare entity for autosomal dominant and sporadic ataxias with only six Indian and one American pedigree of German descent published at present.[2 4 5] The expanded alleles ranged from 55 to 78 CAG repeats, whereas normal alleles ranged from 7–31 repeats. Recently, an allele of even 45 repeats was described in an Indian control subject without any neurological symptoms and with no family history of ataxia.[5] We now present a case of CJD bearing a repeat of 49 CAG copies. The initial symptoms of this patient resembled those described in SCA12 patients. In particular the action tremor in combination with cerebellar signs that preceded the cognitive impairment for four

Table 1 Distribution of alleles at the SCA12 locus among 1029 ataxia patients and 150 healthy controls. Undetected repeat lengths are not shown

	Healthy controls		Ataxia patients	
$(CAG)_n$	Number	Frequency (%)	Number	Frequency (%)
4	–	–	2	0.10
7	1	0.33	1	0.05
9	2	0.67	49	2.38
10	176	58.67	1270	61.71
11	3	1.00	20	0.97
12	1	0.33	3	0.15
13	34	11.33	229	11.13
14	33	11.00	174	8.45
15	37	12.33	244	11.86
16	1	0.33	20	0.97
17	4	1.33	19	0.92
18	–	–	14	0.68
19	1	0.33	2	0.10
20	1	0.33	2	0.10
21	5	1.67	–	–
22	–	–	1	0.05
23	–	–	1	0.05
24	1	0.33	1	0.05
26	–	–	1	0.05
28	–	–	2	0.10
40	–	–	1	0.05
41	–	–	1	0.05
49	–	–	1	0.05

months was striking. On the other hand, ataxia is also a prominent clinical feature of the Kuru-plaque variant found in this patient, which is linked to the MV genotype at codon 129 and PRP^{sc} type 2. However, we cannot elucidate whether CJD of this patient unmasked SCA12 at a subclinical stage or whether the 49 allele is a large and rare normal allele without any influence on the phenotype and, unfortunately, there are no other family members available for genetic evaluation. What remains is the coincidence of two very rare diseases, respectively genetic variations. The protein phophatase PP2A may play a part in tau phosphorylation and apoptosis. Therefore, the possibility that a large SCA12 repeat could influence the pathogenesis of sporadic CJD, especially the Kuru-plaques variant, should be further evaluated.

The role of the 40 and 41 CAG repeats in two sporadic late onset ataxia cases is also difficult to interpret and we cannot exclude a pathogenic influence, although an even larger allele was found in a young Indian healthy control. The findings of this study implicate a more sophisticated interpretation of SCA12 alleles and raise the question about the diagnostic threshold between normal and expanded alleles.

Y Hellenbroich
Institute of Human Genetics, University of Lübeck, Germany

W Schulz-Schaeffer
Department of Neuropathology, University of Göttingen, Germany

Y Hellenbroich, M F Nitschke
Department of Neurology, University of Lübeck

J Köhnke
Institute of Human Genetics, University of Lübeck

G Händler
Department of Radiology, University of Lübeck

K Bürk
Department of Neurology, University of Tübingen, Germany

E Schwinger, C Zühlke
Institute of Human Genetics, University of Lübeck

Correspondence to: Dr Y Hellenbroich, Institute of Human Genetics, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany; hellenbroich@gmx.de

doi: 10.1136/jnnp.2003.028381

References

1 **Holmes SE**, O'Hearn EE, McInnis MG, *et al*. Expansion of a novel CAG trinucleotide repeat in the 5′ region of PPP2R2B is associated with SCA12. *Nat Genet* 1999;**23**:391–2.
2 **O'Hearn E**, Holmes SE, Calvert PC, *et al*. SCA-12: Tremor with cerebellar and cortical atrophy is associated with a CAG repeat expansion. *Neurology* 2001;**56**:299–303.
3 **Parchi P**, Giese A, Capellari S, *et al*. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. *Ann Neurol* 1999;**46**:224–33.
4 **Srivastava AK**, Choudhry S, Gopinath MS, *et al*. Molecular and clinical correlation in five Indian families with spinocerebellar ataxia 12. *Ann Neurol* 2001;**50**:796–800.
5 **Fujigasaki H**, Verma IC, Camuzat A, *et al*. SCA12 is a rare locus for autosomal dominant cerebellar ataxia: a study of an Indian family. *Ann Neurol* 2001;**49**:117–21.

Pre-treatment with corticosteroids and a single cycle of high dose albendazole for subarachnoidal cysticercosis

Cysticercosis is a common parasitic disease of the central nervous system and a pleomorphic neurological disorder. It is an endemic problem in developing countries and is now increasing in industrialised nations.[1] In Mexico neurocysticercosis is one of the main reasons for neurological consultation, and the first cause of epilepsy in adults.[2] The treatment of neurocysticercosis is controversial and depends on the clinical and neuroimaging features, as well as the extent and severity of the associated inflammatory reaction.[3] Basal subarachnoidal cysticercosis and racemose disease of sylvian fissure may behave aggressively producing intracranial hypertension, obstructive hydrocephalus, chronic arachnoiditis, vasculitis, and cerebral infarctions.[4] Subarachnoidal cysticercosis may have a chronic course and a poor prognosis, and is still treated surgically. In a recent open trial of 33 patients with subarachnoidal cysts of at least 50 mm in diameter, treatment with albendazole at a dose of 15 mg/kg/day during 28 days produced an adequate response in 12 patients (36%). The remaining 21 patients (64%) required repeated courses of albendazole and 10 treatments with praziquantel because of a partial or incomplete response to the first albendazole cycle.[5] Repeated treatments are not a minor problem in areas where cysticercosis is endemic and medical resources are limited. To explore a more effective regimen for subarachnoidal cysticercosis we started a pilot study in 1998 with corticosteroids pretreatment and a single course of a higher albendazole dose.

We included 12 patients with the diagnosis of subarachnoidal cysticercosis based in clinical data, imaging studies, and inflammatory cerebrospinal fluid with a positive enzyme linked immunosorbent assay (ELISA) test against cysticercal antigens. After written informed consent six hospitalised patients were pre-treated with intravenous dexamethasone at a dose of 8 mg every eight hours for five days. Four outpatients not receiving corticosteroids were given oral prednisone at dose of 1.5 mg/kg of body weight per day for five days. Two patients with severe arachnoiditis with incomplete response to prednisone, one of them with vasculitis proved by angiography were already receiving cyclophosphamide 100 mg per day, the drug was continued in both and one of them was also pre-treated with oral prednisone as above.

Albendazole was given at a dose of 30 mg/kg of body weight per day in three divided doses for 15 days. As soon as oral intake was tolerated patients taking dexamethasone were switched to prednisone at dose of 1 mg/kg of body weight a day. After four weeks, and depending on the clinical status prednisone dose was tapered individually. Magnetic resonance imaging (MRI) was performed before treatment and three to six months after treatment.

Four men and eight women with an average age of 32.8 years (range 20 to 47) were included. The mean hospital stay for inpatients was 17 days. Table 1 gives symptoms and signs before treatment and at the end of the 15 days of albendazole treatment. In five patients a ventriculoperitoneal shunt was placed before albendazole treatment. In seven patients, corticosteroids improved clinical manifestations within the first 24 hours.

On baseline MRI, the number of subarachnoid cysts varied from 1 to 24 cysts per patient; 10 patients had cysts in the basal cisterns and three had racemose cysts in Sylvian fissure. In three patients additional lobar and subcortical cysts were also present and ependymal or leptomeningeal enhancement was observed in five patients.

On MRI studies at six months of follow up a reduction of 86% of the number of the subarachnoidal vesicles was observed, decreasing from 73 to 10 cysts ($p = 0.02$; Mann-Whitney U test two tailed), with a

Table 1 Changes after treatment in neurological symptoms, signs, and cerebrospinal fluid (CSF) analysis

	Before treatment	After 15 days of corticosteroids and albendazole treatment	
Symptoms	**Number**	**Number**	**p Value***
Headache	11	7	0.115
Nausea	8	2	0.036
Vomiting	7	1	0.027
Blurred vision	3	1	0.590
Somnolence	3	0	0.217
Abnormal mental status	3	1	0.590
Seizures	3	1	0.590
Diplopia	3	0	0.478
Signs			
Intracranial hypertension	11	2	0.001
Papilloedema	10	3	0.012
Abnormal ocular movements	3	0	0.217
Incoordination	2	1	1.000
Motor deficit	1	0	1.000
CSF	**Before treatment**	**At six month follow up**	
Opening pressure mean (SD)	236 (130)	159 (37)	0.018†
Glucose mean (SD)	62 (39)	45 (15)	0.119†
Proteins mean (SD)	73 (94)	97 (117)	0.564†
Cells mean (SD)	70 (133)	59 (110)	0.998†
ELISA+cysticercus antigens	9	12	0.590

*Univariate analysis by Fisher's exact test. †Mann-Whitney U test, two tailed.