ough case collection methods of our study,[3] implies an inconceivably low ascertainment rate for our study of only 32%. It would be reasonable to expect the pattern of notification (by hospital ward registers, general practitioners, and rehabilitation staff) to differ between patients who died and those who did not; separate capture-recapture estimates were therefore calculated for these two groups to obtain a stratified estimate, but their total was similar to the estimate previously obtained.

- If capture-recapture techniques are to be useful for estimating the incidence of stroke, then this should be incorporated into the design of the study
- When using capture-recapture, under-ascertainment is not itself a problem but it is vital that multiple notification of patients is maintained
- Patients should be stratified according to different relative probabilities of being notified by the sources. Strata should be defined in terms of some objective characteristic, rather than by survey results (as we used in the above example)
- Capture-recapture methods have great potential for increasing the efficiency of surveys to estimate the incidence and prevalence of stroke.

At least until we have more experience in the application of capture-recapture, we must continue to attempt complete coverage of cases with stroke registers.

N A TAUB
N LEMIC-STOJCEVIC
C D A WOLFE
Department of Public Health Medicine, UMDS, St Thomas's Campus, London SE1 7EH, UK

Correspondence to: N A Taub, Department of Epidemiology and Public Health, 22–28 Princess Road West, Leicester LE1 6TP, UK.

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Clinical and genetic evaluation of Japanese autosomal dominant cerebellar ataxias; is Machado-Joseph disease common in the Japanese?

Direct mutation analysis for Machado-Joseph disease,[1] dentatorubral-pallidoluysian atrophy,[2] and spinocerebellar ataxia type 1,[3] with which CAG repeat expansions are associated, allows the molecular diagnosis of autosomal dominant cerebellar ataxia (ADCA). Due to the variable clinical manifestations and age of onset in each patient with ADCA, which are correlated with the triplet repeat length,[1-3] it is often difficult to diagnose patients with ADCA from clinical investigations alone, especially distinguishing between Machado-Joseph disease and spinocerebellar ataxia type 1.[4] In Japan, Machado-Joseph disease is considered uncommon and Menzel type of hereditary cerebellar ataxia, which is a clinical entity corresponding to ADCA type I except for Machado-Joseph disease,[5] is often diagnosed, presumably, even in patients with Machado-Joseph disease. Thus the accuracy of the clinical classification of ADCA may be questioned.

We examined a series of 32 patients from 29 Japanese ADCA families, from a region having a population of seven million, to confirm their genetic diagnosis by PCR amplification and re-evaluated their clinical characteristics from the viewpoint of the genotype-phenotype correlation (table). Genomic DNA was extracted from blood cells and each disease locus containing triplet repeats was amplified by PCR. The primers and conditions of the reaction for dentatorubral-pallidoluysian atrophy and spinocerebellar ataxia type 1 have been described.[2 3] For Machado-Joseph disease, we originally designed primers MJ1 (5′-TGATTCGTGAAACAATGTATT-3′) and MJ2 (5′-AGGTAGCGAACATGATGAATG-3′). Products of PCR were electrophoresed on 2% agarose gel followed by ethidium bromide staining or 6% denaturing acrylamide gel with silver stain plus kit (Bio Rad). The repeat length of the expanded alleles was calculated in comparison with the sequenced sample using a video densitometer (Bio-profil system (Vilber Lourmat)).

Eighteen patients from 17 families, constituting 56% of all patients with ADCA, had an abnormal expansion in the Machado-Joseph disease locus with various repeat lengths. The age of onset was highly correlated with the number of repeats ($r = -0{\cdot}79$; $P < 0{\cdot}001$), as reported elsewhere.[1] All patients with Machado-Joseph disease presented with nystagmus and cerebellar ataxia. They also had hyperactive limb reflexes, ophthalmoplegia, and spasticity. Dystonia was prominent in the patients with a longer repeat number and earlier onset. However, amyotrophy and sensory disturbance appear in patients with late onset or severely advanced disease. No involuntary movement was identified. Most of these manifestations were also found in patients with spinocerebellar ataxia type 1.

Summary of the clinical and genetic data on Japanese ADCA

Case	Age/sex	Onset	Ataxia	Deep tendon reflexes	Ophthalmoplegia	Nystagmus	Involuntary movement	Dystonia	Amyotrophy	Sensory disturbance	Spasticity	Epilepsy	Dementia	Clinical diagnosis	Molecular diagnosis	No of CAG repeats*
1	67F	50	+	↑	+	+	–	+	+	+	+	–	–	Menzel	MJD	69
2	47M	30	+	↑	+	+	–	+	+	+	+	–	–	Menzel	MJD	73
3	66M	60	+	→	+	+	–	–	–	+	–	–	–	MJD	MJD	64
4	52F	46	+	↑	+	+	–	–	–	+	+	–	–	MJD	MJD	69
5	48F	35	+	↑	+	+	–	+	–	–	–	–	–	Menzel	MJD	66
6	61M	49	+	↑	+	+	–	–	+	+	+	–	–	Menzel	MJD	65
7	51F	34	+	↑	+	+	–	+	–	+	+	–	–	MJD	MJD	67
8	38M	32	+	↑	+	+	–	–	–	–	–	–	–	MJD	MJD	69
9	42M	24	+	↑	+	+	–	–	–	–	+	–	–	MJD	MJD	74
10	46F	36	+	↑	+	+	–	+	–	–	+	–	–	MJD	MJD	65
11	51F	41	+	↑	+	+	–	–	+	+	+	–	–	MJD	MJD	67
12	51F	33	+	↑	+	+	–	+	+	+	+	–	–	MJD	MJD	73
13	53F	49	+	↑	+	+	–	–	–	–	+	–	–	MJD	MJD	64
14	71M	52	+	↑	+	+	–	–	+	+	+	–	–	Menzel	MJD	64
15	60M	50	+	→	+	+	–	–	–	–	+	–	–	MJD	MJD	66
16	48F	34	+	↑	+	+	–	–	+	–	+	–	–	MJD	MJD	68
17	37F	25	+	↑	+	+	–	+	+	+	+	–	–	MJD	MJD	73
18	48F	40	+	↑	+	+	–	–	–	–	+	–	–	MJD	MJD	68
19	53F	41	+	↑	–	–	–	–	–	–	+	–	–	Menzel	SCA1	
20	28M	17	+	→	+	–	–	–	+	–	+	–	–	Menzel	SCA1	
21	61F	46	+	↑	–	–	–	–	–	–	–	–	+	Menzel	SCA1	
22	47M	43	+	→	–	+	–	–	+	–	–	–	–	ADCAIII	ND	
23	71F	49	+	→	–	+	–	–	+	–	–	–	–	ADCAIII	ND	
24	27M	20	+	→	–	+	–	–	+	–	–	–	–	ADCAIII	ND	
25	39M	30	+	↓	–	SEM	–	–	–	–	–	–	–	Menzel	ND	
26	35M	20	+	↓	+	SEM	+	–	–	–	–	–	–	Menzel	ND	
27	38F	32	+	↓	–	SEM	+	–	–	–	–	–	–	Menzel	ND	
28	55F	50	+	→	–	–	+	–	–	–	–	+	+	DRPLA	DRPLA	
29	46F	38	+	→	–	–	+	–	–	–	–	+	+	DRPLA	DRPLA	
30	30M	19	+	→	–	–	+	–	–	–	–	+	+	DRPLA	DRPLA	
31	28M	12	+	→	–	–	–	+	–	–	–	+	+	DRPLA	DRPLA	
32	29M	14	+	→	–	–	–	–	–	–	–	+	+	DRPLA	DRPLA	

*All samples were heterogenous for the mutations and only expanded alleles were counted.
ND = not determined, cases 25 to 27 were clinically suspected as having spirocerebellar ataxia type 2; SEM = slow eye movement without nystagmus; Menzel = Menzel type of hereditary cerebellar ataxia; DRPLA = dentatorubral-pallidoluysian atrophy.

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The spinocerebellar ataxia type 1 expansions were found in three patients and dentatorubral-pallidoluysian atrophy expansions were found in five. The remaining six patients showed no expansion in any locus. After exclusion of these three types, three patients from two families having pure cerebellar ataxia with retained deep tendon reflexes and slight to moderate atrophy limited to the cerebellum on MRI, were diagnosed with ADCA type III. The remaining three patients from two families were suspected as having spinocerebellar ataxia type 2 because of decreased deep tendon reflexes, slow eye movement without nystugnus and pronounced atrophy in the pons and cerebellum on MRI.

In the nationwide epidemiological study in Japan without genetical evaluation reported by Hirayama *et al*,[5] Machado-Joseph disease occupied only 11% of all ADCA and was regarded as a relatively rare disorder. On the other hand, the Menzel type of hereditary cerebellar ataxia was 49% of all ADCA. Our findings, however, showed that Machado-Joseph disease, which accounted for 56%, is a common ADCA using the genetic estimation. Although the sample size of our study was not large enough to obtain good epidemiological reliability, a significant difference was shown by z test between the results of Hirayama *et al*[5] and our findings on Machado-Joseph disease ($P < 0.002$) and on Menzel type of hereditary cerebellar ataxia ($P < 0.002$), but not on dentatorubral-pallidoluysian atrophy. These differences may be due to the difficulty in clinical diagnosis of Machado-Joseph disease and Menzel type of hereditary cerebellar ataxia. In fact, five patients confirmed as having Machado-Joseph disease in this study were clinically suspected of having a Menzel type of hereditary cerebellar ataxia before the genetic analysis.

In conclusion, Machado-Joseph disease is a common ADCA in the Japanese and epidemiological re-examination of Japanese ADCA is necessary to obtain correct proportions of each genetically diagnosed disorder.

KEN INOUE
TOKIJI HANIHARA
YOSHITERU YAMADA
KENJI KOSAKA
Department of Psychiatry, Yokohama City University, School of Medicine, 3–9 Fukuura, Kanazawa-ku, Yokohama 236, Japan
TOSHIO KATSURAGI
KIYOSHI IWABUCHI
Department of Neurology and Psychiatry, Kanagawa Rehabilitation Centre, 516 Nanasawa, Atsugi 243–01, Japan

Correspondence to: Dr Ken Inoue, Department of Psychiatry, Yokohama City University, School of Medicine, 3–9 Fukuura, Kanazawa-ku, Yokohama 236, Japan.

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Amyotrophic lateral sclerosis after accidental injection of mercury

Mercury has been widely discussed in the pathogenesis of amyotrophic lateral sclerosis.[1 2] We describe a case of amyotrophic lateral sclerosis after accidental injection of mercury.

While shaking a mercury thermometer, a female nurse plunged it into her left hand. Elementary mercury infiltrated into the soft tissues of her palm (figure). The diffusely distributed mercury particles could not be removed completely by surgical means. Two years later, blood mercury concentrations, analysed with atomic absorption spectroscopy, were raised (15 µg/l, reference < 5 µg/l), but declined soon afterwards to normal values.

Three and a half years after mercury infiltration, the 38 year old woman was admitted with progressive weakness of the legs which had begun a few weeks before. She had moderate weakness of the musculature—most pronounced in the lower limbs—slight cerebellar ataxia, and fasciculations in the thighs. Deep tendon reflexes were hyperactive at all her limbs. Babinski's sign was positive on the left. Cranial nerves and sensation were normal. Electromyography showed pathological spontaneous activity in muscles of both legs. Gastrocnemius muscle biopsy suggested neurogenic muscle atrophy. Mercury and lead concentrations in blood, urine, and hair were not raised. Medical history was unremarkable.

With a presumptive diagnosis of amyotrophic lateral sclerosis, we performed a chelation treatment with dimercaptosuccinic acid. Urinary mercury excretion increased (peak value 41·6 µg/24h, reference < 10 µg/24h) without clinical improvement. Muscular atrophy, cramps, and fasciculations become prominent in all limbs. Six months later, a severe bulbar syndrome developed.

Four years after the onset of neurological symptoms, the patient is tetraplegic. Communication is possible via eye movements. There is no respiratory insufficiency, sensory deficits, or dementia.

Mercury accumulates within the CNS, entering either by crossing the blood-brain barrier or via retrograde axonal transport. In our patient, mercury from the deposit in the hand could have slowly accumulated in the CNS over time. This would explain the dissociation between exposure to mercury and onset of clinical symptoms. Initial trauma and repeated surgical interventions may have enabled retrograde axonal transport.

It has been speculated that a pre-existing impairment or a genetically determined dysfunction of motor neuron metabolism could be aggravated by various exogenous factors such as trauma, triggering the manifestation of amyotrophic lateral sclerosis.[3] Thus mercury and trauma could have worked as synergistic factors in our patient.

Chelation treatment, as in this patient, has never been successful in amyotrophic lateral sclerosis. Such treatment—to be of any use—should be initiated shortly after exposure to mercury to prevent an accumulation and irreversible damage within the CNS.

Pure coincidence of a rare disease with an extraordinary preceding event cannot be ruled out, but the unusual appearance of amyotrophic lateral sclerosis in a young woman supports the role of mercury as a causative factor in this case.

In previous reports of motor neuron diseases after mercury incorporation, clinical symptoms developed shortly after the intake of large amounts of mercury and included typical signs of mercury intoxication.[1 2 4 5] Our patient illustrates the possibility that, if present over a longer period of time, relatively small amounts of mercury may cause sporadic amyotrophic lateral sclerosis without other signs of mercury intoxication.

STEFAN SCHWARZ
Department of Neurology, University of Heidelberg, 400 Im Neuenheimer Feld, Heidelberg 69120, Germany
INGO W HUSSTEDT
Department of Neurology, University of Münster, 33 Albert-Schweitzer-Strasse, Münster 48129, Germany
H P BERTRAM
Department of Pharmacology and Toxicology, University of Witten-Herdecke, Herdecke 58313, Germany
KLAUS KUCHELMEISTER
Department of Neuropathology, University of Münster, 33 Albert-Schweitzer-Strasse, Münster 48129, Germany

Correspondence to: Dr Stefan Schwarz.

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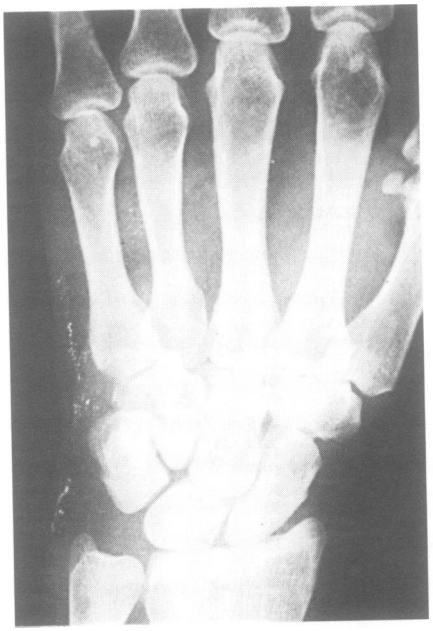

Radiograph of the left hand after injury with a mercury thermometer. Incorporated mercury particles are diffusely distributed in the soft tissues of the palm.

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