excision of a parathyroid adenoma. These sisters were subsequently noted to have large irregular pigmented naevi on their trunks, arms, and legs. These naevi were clinically and histologically consistent with lesions of the dysplastic naevus syndrome.

The father of the three girls also had primary hyperparathyroidism and in 1982 noted that a mole had become indurated and irritant. Histological examination confirmed the diagnosis of nodular malignant melanoma. In neither the father nor the eldest daughter had there been histological evidence of a naevus preceding the malignant melanoma and in neither had clinically abnormal naevi been reported. A fourth sibling was completely healthy.

FAMILY 2

A 15 year old girl presented in March 1983 with a two year history of increasing pigmentation on her wrists, lips, and backs of her hands. She had suffered from eczema and asthma since the age of 2; the eczema had been treated with a moderately potent topical steroid and the asthma with a salbutamol inhaler used intermittently. The dysplastic melanocytic naevus syndrome had been diagnosed in the mother in 1973,⁴ and the mother's father had died from a malignant melanoma that had arisen in a naevus. A maternal aunt had type II diabetes mellitus, and a maternal uncle had pernicious anaemia and type II diabetes mellitus.

Examination of the girl showed hyperpigmentation over the extensor aspects of the joints of both hands and on the fronts of both wrists. The nipples, the buccal mucous membranes, and the linea nigra were also hyperpigmented. There was a postural fall of 15 mm Hg in the systolic blood pressure (110/60 mm Hg supine, 95/60 mm Hg standing). Addison's disease was diagnosed when her plasma cortisol concentration at 0900 was found to be 150 nmol/l (4.9 pg/100 ml) (normal range 170-700 nmol (5.6-22.9 pg/100 ml) and her plasma adrenocorticotrophic hormone concentration at 0900 was 1605 ng/l (normal 10-80 ng/l) and a long test with tetracosactrin acetate (2 mg Synacthen Depot intramuscularly) did not yield a response. Antiadrenal antibodies were present and her HLA type was homozygous for A1, B8, C7, and DR3.

Discussion

The multiple endocrine adenopathy syndrome, in which primary hyperparathyroidism is often a presenting feature, and the autoimmune polyglandular syndrome, in which Addison's disease is a constant feature, are both syndromes of familial endocrine abnormalities. They are inherited in an autosomal dominant mode, and the polyglandular syndrome has been linked with the HLA system.⁵ Multiple endocrine adenopathy may present with tumours of the pancreatic islet cells, neurofibromatosis, and thyroid medullary carcinoma.

The dysplastic naevus syndrome is similarly dominantly inherited, and the association between two dominantly inherited syndromes may be fortuitous. The association between the dysplastic naevus syndrome and families susceptible to cancer has been well reported,³ but no reports have previously been published of a link with multiple endocrine disease. Members of both families reported on here, however, presented with multiple endocrine abnormalities and the dysplastic naevus syndrome.

We thank Dr D Brenton, University College Hospital, for allowing us to report on his patient.

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Trace elements in cerebrospinal fluid in motor neurone disease

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Abstract

Concentrations of sodium, chlorine, potassium, chromium, iron, cobalt, zinc, rubidium, silver, caesium, and selenium in cerebrospinal fluid from 14 control subjects and 20 patients with motor neurone disease were measured by in vitro neutron activation analysis. No statistically significant correlation was found between the concentrations of any two elements other than sodium and chlorine in either the patient or control

group ($r=0.9905$; $p<0.001$). The mean cobalt concentration was significantly lower in the patients ($p=0.0015$). No other statistically significant difference was shown.

The relevance of this finding was examined in relation to current concepts of the pathogenesis of motor neurone disease and the role of cobalt in cellular metabolism.

Introduction

Although the aetiology and pathogenesis of motor neurone disease remain unknown, repeated attempts have been made to implicate heavy metals, notably lead and mercury. While lead poisoning may occasionally produce a syndrome resembling motor neurone disease which improves with chelation therapy, patients with the true disease clearly do not respond to such treatment.¹ Other studies have also tried to show a toxic role for elements such as selenium, manganese, aluminium, calcium, and copper in motor neurone disease.^{1,2} No clear evidence has emerged.

In view of the continuing possibility of a metabolic cause for motor neurone disease we have studied the concentrations

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of trace elements in cerebrospinal fluid. These are crucial for normal enzyme function, and possibly abnormalities might suggest the presence of an enzymatic defect.

Patients and methods

Cerebrospinal fluid was obtained by lumbar puncture from 20 patients with motor neurone disease and 14 controls with functional disorders, headache, or cervical spondylosis. Stainless steel needles were used. Samples were freeze dried and stored at -20°C in metal free plastic containers. Patients and controls were comparable in age and duration of sample storage. The concentrations of sodium, potassium, chlorine, chromium, iron, cobalt, zinc, rubidium, caesium, and selenium were determined by neutron activation analysis. Those performing the analysis did not know which group each specimen came from.

Results

The only element showing a significant difference between the control and patient groups was cobalt (table), the concentration being lower in the patients (Student's t test; $p=0.0015$). As the

Concentrations of cobalt in cerebrospinal fluid ($\mu\text{g/g}$ dry weight)

Controls		Patients	
Subject No	Result	Case No	Result
1	0.156	1	0.173
2	0.128	2	1.570
3	0.073	3	NE
4	0.108	4	0.048
5	0.320	5	0.019
6	0.439	6	0.024
7	0.222	7	0.025
8	0.031	8	0.018
9	0.080	9	(0.026)*
10	0.150	10	(0.013)*
11	0.040	11	0.026
12	0.047	12	0.015
13	0.075	13	0.122
14	0.033	14	0.198
		15	0.042
		16	0.031
		17	0.110
		18	0.034
		19	0.037
		20	0.028

NE = Not estimated.

*Not detected (figures in parentheses are limits of detection).

control data had a log normal distribution, statistical analysis for this element was performed on a logarithmic transformation. We suspect that the high cobalt concentration in case 2 (table) was the result of vitamin B_{12} injections, which had been given unbeknown to us. This result was therefore excluded. There was no correlation between cobalt concentration and age, duration of storage, or cerebrospinal fluid protein concentration.

Comment

We can find no other report of the concentrations of these trace elements in the cerebrospinal fluid in motor neurone disease, although concentrations of zinc, iron, and selenium in the spinal cord³ and of potassium, iron, zinc, and rubidium in muscle⁴ have been described.

Finding reduced cobalt concentrations in the cerebrospinal fluid of patients with motor neurone disease is of great interest. It has been recently suggested that motor neurone disease may result from a defect of one of the enzymatic deoxyribonucleic acid (DNA) repair mechanisms.⁵ Cobalt is closely concerned in nucleic acid biochemistry both in the form of vitamin B_{12} (an essential cofactor for methyltetrahydrofolate oxidoreductase and ribonucleotide reductase) and in the maintenance of nucleic

acid structure. This latter raises the possibility that this finding merely reflects loss of nucleic acid and thus a secondary rather than a primary effect. Zinc and iron, however, are also important structural components of nucleic acids. These showed no significant differences between the patients and controls and this explanation therefore seems unlikely.

An alternative and more likely possibility is that a defective enzyme might either be a cobalt metalloenzyme or depend on cobalt as a cofactor. Probably the observed cobalt deficiency does not simply represent vitamin B_{12} depletion, although this is a cause of myelopathy principally affecting the posterior columns. It should also be noted that cobalt deficiency in sheep is well recognised as causing atrophy and degeneration of cerebral neurones among other features.

It may be that these abnormal concentrations of trace elements in cerebrospinal fluid do not accurately reflect differences in tissue concentrations. Further work is in progress in this department examining both concentrations of trace elements, including cobalt, in tissues and aspects of DNA repair in motor neurone disease.

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ONE HUNDRED YEARS AGO Again has the verdict of a coroner's jury justified the framers of the Infant Life Protection Act, in their opinion that every person receiving a child to nurse, apart from its parents or guardians, should be brought under the provisions of the Act, and be subjected to registration and inspection. We beg to call the attention of the Metropolitan Board of Works, whose duty it is to see that the Act is carried out, to the rider to the verdict drawn up by the jury, calling their attention to "the great necessity for an amendment of that Act, so that it should be made compulsory that any person taking a child to nurse for profit should be registered." We would also draw the attention of the Infant Life Protection Society, under whose auspices the original Act was introduced into Parliament, to this case, with a view to their taking up the subject of an amendment of the Act. The child, in this instance, was put out with an old woman to nurse, 7s. 6d. weekly being paid for it. The woman has no other means of earning a livelihood. She paid 3s. 6d. a week for her room, and on the remainder she had to feed herself and the child. Dr. Day states that "in the stomach of the deceased were some tea-leaves and large pieces of hard biscuit, not even soaked, but looking as if they had been pushed down the child's throat." The sanitary officer said that the room was the worse he had ever been in for filth and wretchedness, and there was no bed in the place. The jury returned a verdict of "Death from exhaustion and from tuberculous disease of the stomach and brain, accelerated by improper feeding and the bad sanitary surroundings in which the deceased lived." If two such children living together with one nurse are not allowed by law to be treated in this manner, why should innumerable units, from one end of the country to the other, be subjected to slow starvation and such fatal insanitary conditions as we see in this case, which is but a type of thousands? (*British Medical Journal* 1884;ii:122.)