Cerebellar calcification and lead

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SUMMARY In elderly subjects who were brought up in a known high lead environment in Queensland, Australia, childhood residence and occupational status provide circumstantial evidence of a relationship between excessive lead intake and cerebellar calcification as seen on computed tomography. This supports experimental and neuropathological studies demonstrating an association between exposure to lead and perivascular cerebellar calcification.

In the first third of this century lead ingestion was a particular childhood hazard in Queensland, Australia, relating to the lead content of the painted railings of the typical wooden Queensland home. Lead ingestion occurred by transfer of lead to the mouth when fingernails were bitten or nails chewed. In wet weather, children also licked raindrops off the railings, attractive because of the sweet taste of lead acetate dissolved in the rain droplets.

Previous work performed in Queensland has indicated indirectly an association between excessive lead intake and cerebellar calcification as seen on CT.^{1,2} Post mortem studies have also shown an association between cerebellar calcification and a raised cranial bone lead content.^{3,4} Available evidence has suggested that cerebellar calcification is an incidental finding unrelated to cerebellar symptomatology.

We have examined a group of patients, previously demonstrated by CT to have cerebellar calcification, for further direct and circumstantial evidence supporting a lead aetiology. To obtain direct evidence of excessive body lead we used a recognised x-ray fluorescence (XRF) technique⁵⁻⁷ to measure their *in vivo* finger bone lead concentration. For circumstantial evidence we have looked particularly at residence in childhood. In addition, since lead ingestion in childhood may result in intellectual impairment with possible consequent low occupational status, we have examined the occupational status of our subjects.

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Received 5 June 1984 and in revised form 5 December 1984.
Accepted 15 December 1984

Methods

Seventeen patients were identified who had cerebellar or both cerebellar and basal ganglia calcification on CT. Patients had undergone CT for a variety of reasons unrelated specifically to the possibility of cerebellar or basal ganglia disease. Information was obtained as to where the patient had spent his childhood and in what sort of house, and what his highest and his father's highest occupational status had been. Finger bone lead estimation was performed using the XRF method.⁵ Blood and urine specimens were collected for the estimation of lead concentration.

Additional subjects with CT cerebellar calcification were derived from a pilot study.¹ All subjects in the pilot study, which included a control group manifesting no calcification, had undergone CT. The pilot study also contained a group of subjects with basal ganglia calcification only. Subjects in the pilot study did not undergo XRF testing. The mean year of birth of calcification and control subjects reported in the pilot study was 1918. The same applied to the seventeen new patients reported on here. Table 1 summarises details of the patients studied.

Results

The new patients studied consisted of 12 males and five females with an average age of 66 years. Evidence of renal impairment and/or systemic hypertension was uncommon and occurred at a frequency close to that found in control subjects.¹

(a) CT Appearances (fig)

Radiating curvilinear calcification, seen as irregular thick bands when extensive, and invariably symmetrically distributed within the cerebellar cortex, was as reported by Graham.² Basal ganglia calcification varied in distribution but occurred mainly as rounded deposits in the caudate nucleus, lentiform nucleus and thalamus. Atrophy was not found more

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Table 1 Summary of patients included in the present study

Source	N	CT findings
1984 patients	10	"Cerebellar calcification & basal ganglia"
Ah Hoon & Price (1980) ¹	7	"Cerebellar calcification & basal ganglia"
	9	"Cerebellar calcification & basal ganglia"
	10	Basal ganglia calcification only
Ah Hoon & Price (1980) ¹	31	"No calcification" controls

Table 2 Childhood residence in Queensland

Queensland Residence	Yes entirely	Partially	Not at all
Cerebellar calcification*	29	2	1
Basal ganglia calcification only†	6	1	2
All subjects with calcification (by addition)†	35	3	3
Controls‡	15	4	12

*Compared with controls, Kendall's Tau = 0.399 $p < 0.001$

†Compared with controls, Kendall's Tau = 0.461 $p < 0.001$

‡For one subject in each of these groups residential information was not available

often in subjects with calcification than in controls.

(b) Childhood residence

Results are shown in table 2, where the "cerebellar"

Table 3 Type of house lived in during childhood

	Brick or stone	Wood Enclosed	Wood open verandah	Not known
Cerebellar calcification*	0	7	24‡	1
Basal ganglia calcification (1 not known)	1	1	6	1
All subjects with calcification† (by addition)	1	8	30‡	2
Controls (1 not known)	10	11	9	1

*Compared with controls, $X^2 = 17.38$, $df = 2$, $p < 0.01$

†Compared with controls, $X^2 = 18.28$, $df = 2$, $p < 0.01$

‡One of these had lived in a stone house surrounded by an open verandah with painted railings.

group includes some with calcification in both cerebellum and basal ganglia (this also applies to tables 3 & 4). Table 2 indicates a highly significant relationship between childhood residence in Queensland and calcification on CT scan. As the amount of an individual's childhood spent in Queensland rises, so does the incidence of cerebellar calcification.

(c) Type of house lived in during childhood

It should be noted that the typical wooden Queensland home is a form of domestic architecture also found in other Australian States (particularly in Northern New South Wales). In table 3 data relating to the type of house lived in during childhood are presented. Since there is a high correlation between childhood residence in Queensland and living in a wooden home with an open verandah, it is not surprising to find the relationship between calcification and being brought up in Queensland continuing to hold here.

(d) Occupational status

In general higher intellectual capacity will lead to the attainment of higher occupational status. In

Fig 1 (a) Moderate bilateral cerebellar calcification found incidentally in a patient with a temporal lobe haematoma. (b) Gross bilateral cerebellar calcification. (c) Bilateral thalamic calcification (arrowed).

Table 4 Occupational status

	(High)	3·5	4·0	4·5	5·0	5·5	6·0	6·5	7·0	7·5	(Low)
Cerebellar calcification*		0	0	0	0	2	4	10	4	4	
Basal ganglia calcification		0	1	0	0	0	1	5	0	1	
All subjects with calcification† (by addition)		0	1	0	0	2	5	15	4	5	
Controls		1	1	2	3	2	6	10	2	1	

*Compared with controls, Kendall's Tau = 0·337 p < 0·01

†Compared with controls, Kendall's Tau = 0·308 p < 0·01

table 4 the occupational status of calcification subjects is compared with that of controls. For this purpose, the occupational status of each subject has been converted to a number, using the ranked tabulations of Congalton.*

All describing themselves as housewives have been excluded (this applies also in section (e) below). In the control group, the mean occupational score for subjects born outside Queensland was very close to that of subjects born in Queensland. To a significant extent, those with CT calcification had failed to achieve as high an occupational status as control subjects.

(e) Fathers' occupational status

A second way of examining a possible effect on intellectual status is to compare the occupational status of each subject with that achieved by his (or her) father. When this was done for control subjects, no decline from father to offspring was evident. When carried out for calcification subjects, there was found a highly significant decline from the occupational status of the father to that of his offspring (using Wilcoxon's signed rank test, $Z = 3·894$, $p < 0·001$). Neither this result, nor that depicted in table 4 can be explained by relating it to the sex of the patients, which is important because of the low occupational status of women during the period under consideration. However, mean scores for male and female subjects were close to each other both for control and calcification groups. Mean scores for their fathers' occupational status were almost identical in the two groups.

(f) Co-ordination and motor disorders

No subject had a history of co-ordination or other motor problem specifically suggesting cerebellar pathology.

(g) Blood, urine and finger bone lead concentrations

Using 50 µg per 100 ml in blood and 80 µg per litre in urine as upper limits of normal, no patient was found to have abnormally raised blood or urine lead levels. Four of the seventeen patients had detectable finger bone lead, levels greater than 25ppm being detectable by the method used.

Each of the 17 patients subjected to XRF testing was matched with two subjects from a study of 200 healthy Queensland residents reported elsewhere,⁹ except for one subject, a man aged 80 yr for whom no match was available. His XRF result was negative. Matching was carried out on the basis of sex, age within 3 years, place of residence in childhood, and freedom from occupational exposure (none of our patient sample had been occupationally exposed to lead).

Of the patient sample, four of 16 had raised finger bone lead as measured by XRF compared with five of 32 of matched healthy subjects. The difference between the calcification patients and the healthy Queensland residents is not significant.

Discussion

Tonge *et al*³ made the original observation of a high level of microscopically evident cerebellar calcification in coroner's necropsies performed in Brisbane, Queensland. Their descriptions of the distribution of calcification, with mild cases showing deposits in the deepest parts of the interfolial sulci near the horizontal fissure, and more severe cases showing extensive calcification around the horizontal fissure and extending laterally in the deeper layers of the folial sulci over both the superior and inferior semilunar bodies, correlate well with the macroscopic distribution as seen on the CT scans and occasionally on plain skull radiographs.² Saal *et al*,⁴ in another necropsy-based study carried out in Brisbane demonstrated the intimate anatomical relationship of calcium deposits to the cerebellar blood vessels. Tonge *et al*³ refer to the characteristic lesions being found in a child of 8 years who had died of lead nephritis.

Experimental evidence, especially in rats,^{10,11} indicates a particular susceptibility of the cerebellum to deposition of calcium following exposure to excessive lead with particular implication of the cerebellar capillaries.¹²⁻¹⁴ It is not that lead accumulates preferentially in the cerebellum compared with other parts of the brain, but rather that the capillaries there are more susceptible to it.¹⁵

Distribution studies have indicated a particular

predilection of brain endothelial cells to accumulate lead.¹³ Younger animals are particularly susceptible. Thus whereas continued exposure of the adult rat brain to lead results in a plateau in brain lead content, in very young animals the lead content continues to rise. Furthermore, when endothelial cells have been exposed to lead they accumulate not only lead but also calcium.¹⁵ Lead decreases the affinity of brain mitochondria for calcium¹⁶ and it has been suggested that this accounts for the increase in calcium concentration found in brain cytosol. Thus there are good reasons from neurochemical studies to relate lead exposure to the presence of calcium in the walls of cerebellar capillaries.

There is insufficient data on which to draw a definite conclusion as to whether basal ganglia calcification alone might relate to lead ingestion. Of data presented in tables 2-4 only that of table 3 supports a relationship statistically (Kendall's Tau = 0.316, $p < 0.05$). Data from tables 2 & 4 both tend to favour such an association as does data relating to fathers' occupational status, but not at statistically significant levels.

If lead does result in cerebellar calcification then our failure to find it more frequently in finger bone on XRF testing in our patients compared with healthy subjects resident in Queensland has to be contrasted with its detection in bone by Tonge *et al*³ in subjects showing cerebellar calcification at necropsy. Tonge found cranial bone lead of greater than 41ppm in two thirds of cases where cerebellar calcification was found at necropsy. Not excluded were those with an occupational history of lead exposure or those who might have died of lead nephropathy and come to necropsy for this reason. However it would still seem very likely that the levels of lead in cranial bone at necropsy were greater than the amounts of lead found in the finger bone of our extant patients.

It should be noted also that cranial bone lead levels were greater than 41ppm in over one fifth of those of Tonge's subjects who had died in Queensland without cerebellar calcification (in 74 out of 311). In our sample of matched healthy subjects, only two of 32 had finger bone lead values above this level. This difference between Tonge's results and ours, although statistically significant, is not decisive since the exclusions noted above have not been made from Tonge's data.

Direct evidence of a previously excessive body load of lead is difficult to obtain *in vivo*. It has been shown¹⁷ that the mean life of lead in blood is approximately 36 days and in soft tissues about 40 days so it is very much as expected that no significant blood or urine lead was found in our subjects. Such measurements will clearly only detect recent, not remote,

exposure to lead. Ninety five percent of body lead is found in bone with a biological half-life for lead in the bone pool of 10^4 days (27 years). Assuming excessive lead absorption occurred in childhood the measurable amount of bone lead represents the residue of more than two biological half-lives of bone lead since the average age of our patients was 66 years. However, several researchers¹⁸⁻²⁰ have found significant differences in the lead content of different human bones with greater concentrations in the femur and tibia than in the ribs or vertebra and even between the inner and outer skull tables. It may be that there is more rapid turnover of lead in fingerbone (which we studied) than in cranial bone studied by Tonge and that this could well explain the discrepancies in bone lead content in the two studies.

It is worth noting that Tonge *et al*³ examined the cerebella of 44 patients who, at necropsy, fulfilled diagnostic criteria for a diagnosis of lead nephropathy. In 37 (84%) of those subjects cerebellar folial calcification was present.

Even if, as we argue, lead is the cause of cerebellar calcification can we be sure that low occupational status does not result from pica? In the pica situation, low intelligence would predispose to the ingestion of lead (because of the mouthing of lead containing objects) rather than result from it. We cannot rule this out but would point to the typical highest Queensland home in the early years of this century as a high lead environment, lead induced acute nephritis having occurred there on a massive scale.²¹ Sayre *et al*²² have suggested that the normal hand-to-mouth activity of young children may be sufficient to account for considerable lead absorption in a high-lead environment without the need to invoke pica as a cause and this may apply here. A study carried out in Queensland as long ago as 1904²³ provides data of relevance to this point. Of closely studied children who had ingested lead, only one gave evidence of pica, while 13 were either nail biters or finger or thumb suckers.

Legislation was introduced into Queensland in 1922 restricting the application of lead paint to surfaces accessible to children. As a result the incidence of lead induced nephritis, previously very high had fallen sharply by the mid 1930s.²¹ If, as we suggest, lead is the agent responsible for cerebellar calcification, then the reduced lead hazard resulting from this legislation may explain why such calcification is now seen only in older subjects. One would predict that it will become increasingly rare over the next two or three decades as fewer and fewer subjects from the generation of children most exposed to lead remain alive.

Although the CT appearances described above

may be rare outside Australia, we would suggest that when the appropriate pattern of cerebellar calcification is seen on CT, then a lead aetiology should be seriously considered.

We are happy to acknowledge our gratitude to Dr R Ah Hoon for access to data collected by him, to Dr JI Tonge and Professor H Baddeley for helpful discussion and to Dr BJ Thomas for carrying out XRF measurements.

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