

Asymptomatic cerebral calcification – a previously unrecognized feature

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Summary: While investigating the radiological appearances of globus pallidus calcification in an autopsy case, cortical-pia mater calcification was detected. There was no documentation of its existence in the literature of radiology, neurology and neuropathology. To establish its incidence and clinical significance, 20 consecutive autopsy brains (15 males, 5 females, age 32–73 years, mean age 56.7) were studied with high resolution radiography and histology. Clinical records, autopsy findings, in-life plain skull films and computed tomography of the brain (if available) were reviewed. Radiologically, the calcifications appeared as 1–2 mm irregular spots or tiny pin-point opacities in the pia mater and subcortical regions, either unilaterally or bilaterally in the frontal (15 cases), temporal (15), parietal (3) and occipital lobes (1). Similar calcification was detected in 1 of the 3 in-life computed tomographic scans available. Histologically, these cortical-pia mater calcifications were extracellular amorphous calcified masses of various sizes in necrotic neural tissue, frequently associated with microscopic haemorrhage and hypoxic neuronal changes in the adjacent brain tissue. Blood vessels in the region were not hyalinized or calcified. The occurrence was not related to age. Hospital stay was < 7 days in 14 and < 30 days in 2; 50% of patients died within 48 hours after admission. None of the patients had records of long term cytotoxic chemotherapy, radiotherapy or central nervous system infection. Two had stroke, one had cerebellar atrophy and one mild hypercalcaemia. The high incidence of calcifications in the temporal lobes, while asymptomatic, suggests that cortical calcification may be a pointer to the aetiology of idiopathic epilepsies in the elderly.

Introduction

The normal or asymptomatic intracranial calcifications have been well documented by plain films of the skull and subsequently computed tomography (CT) and include pineal, calcifications in the habenula, choroidal plexus, falx and Pacchionian granulations as well as the basal ganglia especially in the globus pallidus. While investigating the appearances of globus pallidus calcification of an autopsy case by high resolution radiography for correlation with in-life CT, cortical calcification was detected. Subsequently, a total of 20 autopsy brains were examined, of whom a large number were found to have this type of calcification. A literature search failed to elicit a similar report.

Materials and methods

Twenty consecutive 20% formalin fixed human autopsy brains were examined by plain film radio-

graphy and relevant areas subjected to histology. Each brain was sectioned at 1 cm intervals in the axial plane corresponding to a computed tomography examination. The brain slices were radiographed with an overcouch tube using a standard screen-film combination. The films were viewed and brain sections chosen for high resolution soft tissue radiography using a mammography unit* (Figure 1). Having localized the calcifications, the relevant area of brain was removed and slices of approximately 1.5–2 mm thick were cut parallel to the axial plane and again radiographed (Figure 2). Representative thin tissue blocks were processed for histological examination.

The various types and sites of calcification were recorded as seen on the initial films, the high resolution films of the axial brain slices and of the selected 1.5–2 mm thick tissue sections. Special attention was paid to pial and cortical calcification, but other calcifications were also recorded when

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*Siemen's manomat E with a molybdenum tube using Kodak Min-R (single back) screen with Kodak Ortho M (single coated film).

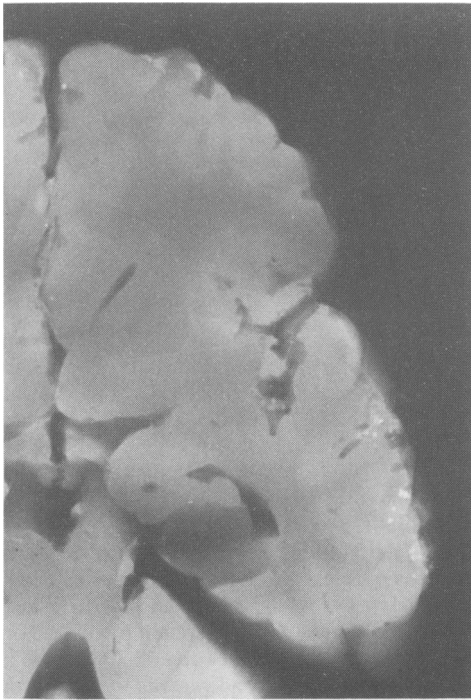


Figure 1 On a high resolution soft tissue film of a 1 cm thick section, there are cortical calcifications particularly in the temporal lobe but also in the frontal lobes. Some of the calcifications are quite large, i.e. about 1–2 mm, but most are considerably smaller and more numerous.

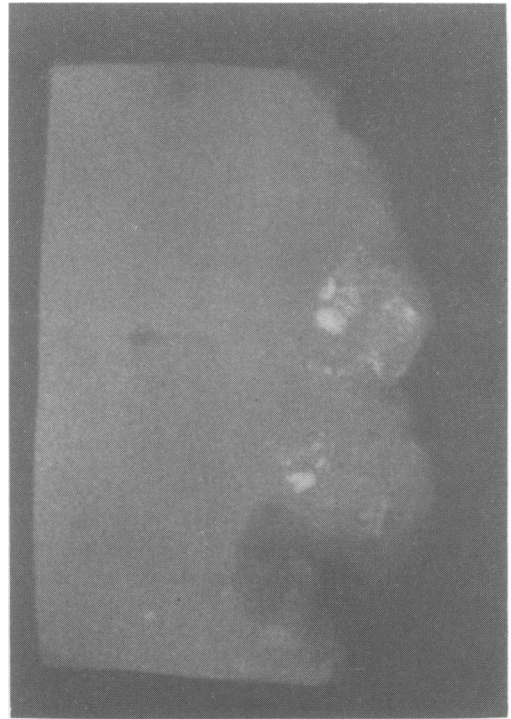


Figure 2 In similar type radiograph of a 1.5 mm thick tissue block taken for histology the calcifications are clearly within the cortex as well as on the surface. The large and small calcifications can be distinguished.

present including pineal, habenula, choroidal and globus pallidus.

The histology sections from all brains were randomized, labelled with a code number, and read by the pathologist. Notes were taken on the morphology of calcification, whether it was intra- or extracellular, its location in the nervous tissue, pia mater, blood vessel wall, and associated tissue changes such as necrosis, neuronal loss and haemorrhage. The pathological findings were then interpreted in the light of radiological findings, clinical history and autopsy findings.

The clinical case notes were carefully scrutinized for central neurological signs and symptoms and the autopsy examinations of the brains were noted.

Results

Sex and age distribution (Table I)

There were 15 males and 5 females, 11 were under the age of 60, the youngest, a female, was 32 and the oldest, a male, was aged 73.

Length of hospital stay prior to death (Table I)

Ten patients (50%) were in hospital for less than 48 hours and 14 (70%) less than 1 week. Only one patient was in for 1 month.

Clinical background and cause of death (Table I)

No common clinico-pathological factor emerged from a scrutiny of the notes or from the autopsy. There were 4 patients with myocardial infarction, 4 with pneumonia or bronchopneumonia, 5 with tuberculosis, 4 with a variety of infections, and 5 with malignancies (all 3 lymphomas were post-mortem diagnoses). No patient had received cranial radiotherapy or prolonged multiple cytotoxic chemotherapy. Serum calcium level was available in 12 patients. The adjusted calcium was within normal limits in 8 cases, low in 3 and slightly increased in 1 (patient No. 18). Phosphate levels were normal in all cases. Only 4 patients had clinical neurological symptoms and signs: 2 with stroke (Nos. 11, 12), 2 with severe hypoxic brain damage (Nos. 8, 13) confirmed by brain CT, and 1 with lymphoma (No. 17) presented with acute confusion and fever of unknown origin.

Table I Clinical details, serum calcium and site of radiographic calcification

Patient No	Sex	Age	Cause of death, clinical background	Serum calcium mmol/l (normal 2.13–2.51 mmol/l)		Radiographic calcification			Hospital stay
				NA		C-p FR T Bil	Pi	Art	
1	M	37	Uncontrolled bleeding, from multiple lacerations in liver, ileum, colon	NA		C-p FR T Bil	Pi	Art	<24 h
2	F	41	Carcinoma stomach, metastases in lung, liver, lymph nodes, ovary	NA		C-p FL TR	Art	Ch-pl	<24 h
3	M	72	Extensive myocardial infarct, lobar pneumonia	2.15		C-p FBil OBil	Art	Ch-pl	H <24 h
4	F	51	Bronchopneumonia, lymphoma, mitral valve stenosis	1.95		C-p FBil TBil	Pi	Art	Ch-pl <24 h
5	M	63	Acute myocardial infarct	NA		C-p TR PL	Art	Ch-pl	<24 h
6	M	58	Pseudo-membranous colitis, surgery for spinal cord compression	2.20		C-p TL FBil			6 days
7	M	57	Lobar pneumonia, multiple myeloma, active pulmonary tuberculosis	2.31		C-p TBil		Ch-pl	H 23 days
8	F	32	Non-Hodgkin lymphoma with multiple organ involvement, CMV infection in lungs, hypoxic brain damage on CT	2.18		C-p FL		Gl-p Bil	11 days
9	M	57	Nasopharyngeal abscess, bronchopneumonia, pulmonary tuberculosis	1.96		C-p PR	Pi	Art	Ch-pl 9 days
10	M	44	Acute myocardial infarction	2.10		C-p TBil	Pi	Art	<12 h
11	M	73	Hypertensive cerebral haemorrhage	NA		C-p FBil	Art	Ch-pl	<48 h
12	F	62	Hypertensive cerebral haemorrhage. Left renal artery stenosis, left atrophic kidney, ischaemic heart disease	NA		C-p TR FR		Ch-pl	H <12 h

Continued overleaf

Table 1 continued

Patient No	Sex	Age	Cause of death, clinical background	Serum calcium mmol/l (normal 2.13-2.51 mmol/l)	Radiographic calcification					Hospital stay	
13	F	51	Hypoxic brain damage on CT, cerebellar atrophy, suicide	2.46	C-p T Bil F Bil	Pi	Art	Ch-pl	Gl-p	Bil	ITU 5 days
14	M	73	Extensive myocardial infarction, severe atherosclerosis of aorta	NA	C-p FR TR	Pi	Art	Ch-pl	Gl-p	Bil	< 12 h
15	M	68	Miliary tuberculosis (pulmonary, adrenals, hilar lymph nodes). Gastrectomy, splenectomy - old	2.13	C-p FL T Bil	Pi	Art	Ch-pl	Gl-p	Bil	7 days
16	M	67	Large pulmonary embolism, post-hip surgery, deep vein thromboses in both calves, pulmonary tuberculosis.	NA	C-p F Bil TL	Pi	Art	Ch-pl	H		11 days
17	M	67	Non-Hodgkin lymphoma, presented with acute confusion and fever	2.37	C-p P Bil		Art	Ch-pl	H		27 days
18	M	56	Tuberculosis (pulmonary, epididymal and prostatic)	2.89	C-p F Bil TR	Pi	Art	Ch-pl			< 24 h
19	M	73	<i>Escherichia coli</i> septicaemia, left acute pyelonephritis, diabetes mellitus, macronodular cirrhosis, portal hypertension	2.32	C-p FL TR			Ch-pl	H		4 days
20	M	32	<i>Staphylococcus aureus</i> septicaemia, multiple lung abscesses, deep vein thrombosis (left popliteal femoral and iliac veins), drug addict	NA	C-p FL TL			H			2 days

C-p: cortical-pia mater; F: frontal lobe; R: right; T: temporal lobe; Bil: bilateral; Pi: pineal; Art: arterial/arteriolar; L: left; Ch-pl: choroid plexus; O: occipital lobe; H: habenula; P: parietal lobe; Gl-p: globus pallidus; NA: not available.

Radiographic calcifications (Table I)

Cortical-pia mater calcification could be identified in all cases on the radiographs. In 16 the calcification appeared sufficiently deep to be confident that it was in the cortex and was confirmed on thin slices. The calcifications appeared to be either spots of 1–2 mm or tiny pin-point calcifications (Figures 1 and 2). The calcifications occurred most commonly in the frontal region and were frequently bilateral (13 cases) and symmetrical (8 cases). Globus pallidus calcification was found in 4 cases aged 32, 51, 68 and 73 years. Arterial calcification in 14, pineal in 9, habenular in 9 and in the choroid plexus in 15. CT brain scans were performed in-life on 3 of these patients, these scans were reviewed and in one there appeared to be similar cortical calcifications (Figure 3a,b).

Pathology

On gross examination all but 3 cases were normal. Cerebral haemorrhage in the thalamo-striate area was present in 2 and cerebellar atrophy in 1 and grittiness during cutting occurred in only 2 brains, both with heavy blood vessel wall calcification in the basal ganglial region. Laminar necrosis was not apparent and cortical-pia mater calcifications were not visible.

Histologically, there were two patterns of calcification in 89 sections, the peripheral pattern (cortical-pia mater) and the central pattern (in the basal ganglia).

The cortical-pia mater calcifications were composed of large amorphous patches of calcium deposit of various sizes, shapes and density in nervous tissue (Figure 4) in the deep layers of grey matter or in the perivascular spaces of the pia mater and Virchow's spaces, and frequently associated with microscopic haemorrhages. Hypoxia neuronal changes were evident in the preserved areas. There was no blood vessel calcification in the region.

In the central pattern there were small spherules of various sizes in the extracellular spaces or around capillaries and conglomerations of spherules formed multilobated calcifications (Figure 5). No tissue degeneration was visible on light microscopy. Calcification in the media of blood vessels was common.

Discussion

Soft tissue calcification is usually classified as dystrophic and metastatic, the latter said usually to be associated with a metabolic abnormality especially hypercalcaemia. Most intracranial calcifications such as pineal, choroid plexus, falx cerebri

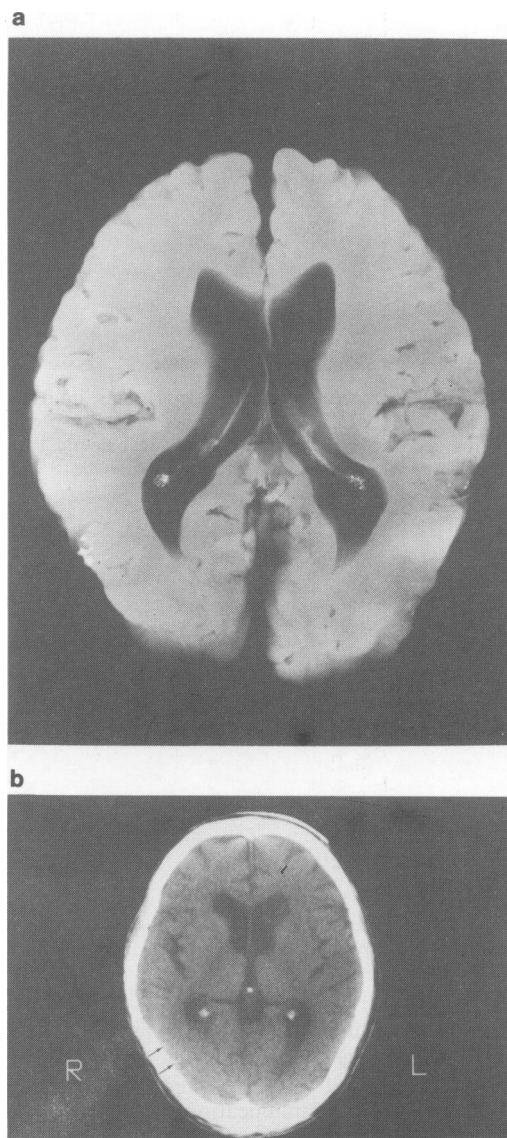


Figure 3 a, There are a small number of large calcified spots in the right posterior parietal region and smaller ones on the left. The bilateral calcifications in the choroid plexus stand out more clearly, being contrasted against the air in the lateral ventricles of the 1 cm thick brain section. b, A CT section of the same patient at approximately the same level shows small densities (arrow) in the same region suggesting the presence of calcifications.

and globus pallidus are common, well recognized, more frequent in the middle aged and elderly, and are considered as 'physiological' dystrophic calcification.¹ Pathological dystrophic calcification is less common but has well established associations

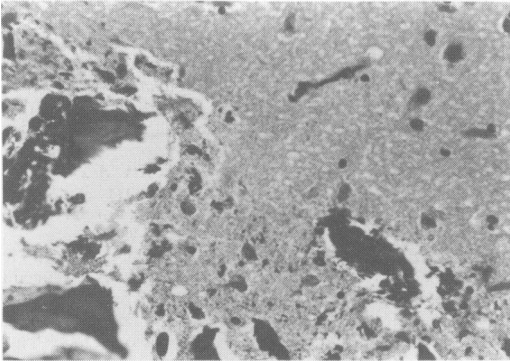


Figure 4 In cortical-pia mater calcifications, both fine, granular and coarse irregular calcium deposits are present in the necrotic brain tissue. The adjacent neural tissue shows hypoxic changes (Haematoxylin & eosin, $\times 170$).

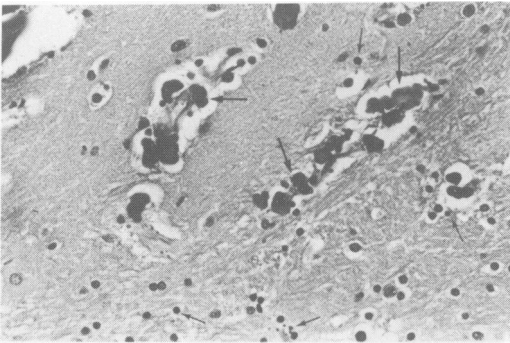


Figure 5 In the basal ganglia, calcification appears as tiny spherules (large arrows) surrounding capillaries and scattered in the neuropil (small arrows) (Haematoxylin & eosin $\times 170$).

with parasitic infestations, infections, particularly with tuberculosis and cytomegalic virus, previous haemorrhage and tumours. Since 1975 there has been a spate of communications concerning cytotoxic chemotherapy and radiotherapy as a cause of cerebral dystrophic calcification in children with acute lymphoblastic leukaemia.²⁻⁵ Encephalitis⁶ and Fahr's disease^{7,8} and meningio-angiomas⁹ have also received attention. None of the cases presented in our series had evidence to suggest any of these conditions.

The cortico-pia mater calcification described in this paper has the features of dystrophic calcification being associated with degenerate nervous tissue and microscopic haemorrhages. Histologically, the cortical-pia mater calcifications are large, randomly distributed, irregular masses with no regional blood vessel calcification, in contrast to the predominantly perivascular tiny calcospherules and heavy blood vessel calcification in our globus pallidus calcification group and in most of the

reported cases cited. A progressive microangiopathic process appears to be the main pathogenetic factor in the latter group. In the former group, the anatomical site, necrosis of the deep layers of the grey matter, and associated microscopic haemorrhage are suggestive of hypoxic laminar necrosis from a global ischaemia in the central nervous system;^{10,11} however, calcification is not mentioned. Clinically, only one patient had a known period of hypoxia though possibly the patients with cardiovascular disease may have been similarly affected.

It is most unlikely that the patients who died soon after admission could have produced cerebral calcifications associated with their acute illnesses and only two patients had cerebral haemorrhage and one cerebellar atrophy. These previous central nervous system conditions were not a particular feature either clinically or at autopsy.

Whilst it is surprising that a literature search going back to 1965 and a review of several neuropathology and neurology textbooks found no description of similar brain calcifications, this may be because it is considered clinically irrelevant. As far as we could determine, there were no signs or symptoms to suggest the presence of these abnormalities. Also, with routine autopsy brain examination without radiographic examination of the brain slices, the cortical-pia mater calcifications would have remained undetected as they are not visible to the naked eye.

As the temporal lobe was so commonly involved it is just possible that these calcifications may be a pointer to the aetiology of idiopathic epilepsy. Epidemiological surveys suggest an increased incidence of idiopathic epilepsy with age¹² up to 77 per 100,000 in those over 60 years old¹³ and these calcifications may prove to become more marked with age, possibly being accumulated after each episode of severe illnesses.

It is, however, not surprising that these calcifications are not visible on computed tomography as they are small and close to the bone and are unlikely to be shown by magnetic resonance imaging as calcification produces signal void.

The calcifications in the globus pallidus are well recognized and, while of interest in their own right, are only marginally relevant to this communication, the investigation having been started because of its recognition on CT and an attempt to show the calcification in greater detail.

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