Fifth day fits: an acute zinc deficiency syndrome?

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SUMMARY A 3-year prospective study to elucidate
the cause of fifth day fits was carried out. A highly
significant relationship with low cerebrospinal
fluid zinc levels was found. Theoretical and practical
considerations support the contention that fifth day
fits are caused by an acute deficiency of zinc.

Convulsions occurring around the fifth day of life in
otherwise normal babies have aroused considerable
interest because of an apparent rise in incidence
and also because the aetiology is unknown. Our
hospital experience during the periods 1971–74
(12 904 live births) and 1975–77 (13 304 live births)
showed a rise in the overall incidence of neonatal
convulsions from 2 to 6 per 1000 live births while the
incidence of fifth day fits rose from 0·6 to 2·2 per
1000 live births. A prospective study was started in
July 1978 to define the syndrome and identify
possible causes.

Method

The fifth day fitters (group 1) were defined as being
normal term babies of appropriate size for gesta-
tional age who developed short-lived and otherwise
unexplained convulsions towards the end of the
first week of life. They were compared with a group
of fitting babies (group 2) in whom a cause for
convulsions had been provisionally identified or
in whom there was some other health problem (such
as being small for gestational age) even if not
obviously related to the convulsions. For further
comparison a group of babies (group 3) was incor-
porated into the study in whom there had been
no convulsions although lumbar punctures had been
performed for other indications—for example
suspicron of sepsis. From the start of the study all
specimens of cerebrospinal fluid (CSF) from groups
1, 2, and 3 were frozen and stored until required for
screening programmes.

Most (87%) of the fifth day fitters were breast fed.
This accurately reflects the pattern in our hospital
where about 90% of term babies are wholly or
primarily breast fed on discharge at day 7.

All babies who convulsed had the following
studies carried out: full blood examination, blood
glucose, serum sodium, calcium, phosphate, mag-
nesium, acid-base estimations, serum proteins,
serum IgM, metabolic screen of urine and blood,
CSF microscopical examination and bacterial
culture, skull x-ray film. A full antenatal and
perinatal drug history was recorded together with a
postnatal drug and feeding history of both mother
and baby. Initially all babies had viral cultures of
CSF, blood, urine, and faeces, and either a com-
puterised tomography scan or ultrasound examina-
tion of the brain. Because few results were
significant these tests were later reserved for babies
with specific clinical indication of viral infection or
a structural brain abnormality. If clinically
indicated further elucidation of metabolic ab-
normalities was done. Several babies had a trial of
pyridoxine without success.

The time of onset of the fits suggested an en-
vironmental influence; furthermore, it was noted
that while all the cases of fifth day fits came from
the standard postnatal nurseries there appeared to
be no such unexplained convulsions among babies
in the special care nurseries. Comparison of nursing
management between the two areas showed that
those babies in the standard postnatal nurseries
received smaller volumes of feeds, more exposure to
Phisohex (3% hexachlorophane), and less exposure to
zinc ointment than those in the special care nurseries.
The last observation prompted us to study the
levels of zinc in the CSF. Estimations of CSF zinc levels
were carried out by an independent laboratory and
were not identified to any group. Analysis was by
flame-aspiration atomic absorption spectroscopy.

Investigation of the air-conditioning system
throughout the hospital showed no source of
infection or toxins. Testing for hexachlorophane
showed no detectable amounts in the CSF specimens
of any in the three groups. Attempts at screening
specimens of CSF for possible toxins using liquid
gas chromatography were unsatisfactory because of
difficulties in developing standard curves for all
the potential toxins.

Results

CSF zinc levels were examined (Figure) and a non-
parametric comparison made between group 1
(fifth day fitters) and groups 2 and 3 (controls) based
on the number of CSF zinc levels above or below
1 μmol/l. (With the skew distribution for CSF zinc
levels it is not appropriate to use a t test or analysis
of variance to compare group means.) Thus only 5 (20%) of 25 babies in group 1 had CSF zinc levels above 1 μmol/l compared with 41 (64%) of 64 babies in groups 2 and 3. Analysis of this 2 × 2 table showed a highly significant tendency ($\chi^2$, >14·0, $P<0.0001$) for CSF zinc levels to be lower than 1 μmol/l more often in group 1 than in groups 2 and 3 (relative risk = 8·2). A normal mean CSF zinc level has been given as 3·7 μmol/l.8

Discussion

These data suggest that unexplained fits occurring around the fifth day may be caused by transient zinc deficiency. Although zinc deficiency has not hitherto been recognised as a cause for convulsions, certain neurological abnormalities4 have been ascribed to zinc deficiency, most of them of a chronic nature. These include loss of taste and smell, depression, irritability, behavioural abnormalities, nystagmus, and optic neuritis. Perhaps an acute deficiency of zinc would have more striking manifestations.

Absorption of zinc in the newborn is believed to be facilitated by zinc-binding ligands in the breast milk which diminish after a few days and zinc-binding ligands in the gut mucosa which take some days to be fully developed.5 Under these circumstances zinc absorption is likely to be lowest towards the end of the first week of life. Zinc is better absorbed from breast milk than from artificial feeds.

However, variations in the quality and quantity of the milk ingested are far greater in breast-fed than artificially-fed infants and may account for further variation among babies.6 The level of calcium in the feeds also affects the absorption of zinc, with high concentrations of calcium having an inhibitory effect. It is not known whether greater volumes of feeds or external applications of zinc ointment give any protection against acute zinc deficiency. With further development of mucosal zinc-binding ligands in fifth day feeders, improved absorption of zinc with spontaneous resolution of symptoms might be expected.

We did not attempt to reverse the syndrome by giving zinc; indeed it may be difficult to prove that zinc deficiency is a cause of fifth day fits, firstly because the convulsions are short-lived, and secondly because it is not known how long it takes for either orally or parenterally administered zinc to become biologically available in the central nervous system. As the fits respond readily to standard treatment the use of experimental measures was not justified. As plasma zinc levels vary with the serum albumin level and fall within hours of stress it was felt that CSF levels of zinc were a more accurate reflection of 'neurologically available' zinc than were plasma estimations. No other types of zinc estimations were carried out. Parameters such as white blood cell zinc are thought to be a more accurate reflection of total body zinc than plasma or CSF levels. However, their relevance in this context is unknown, particularly as the proportion of zinc in the various body compartments may change rapidly over the first weeks of life.

Further studies are planned to correlate zinc levels in artificial feeds and human milk with the occurrence of fits, to investigate the relevance of concomitant calcium levels in the feeds, and to assess the effects of feeding schedules and of the external applications of zinc cream on the incidence of the syndrome.

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Renal pseudotumours caused by xanthogranulomatous pyelonephritis

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SUMMARY
Five cases of xanthogranulomatous pyelonephritis are described. Wilms’ tumour was suspected preoperatively in 2 of the cases and a renal tumour appeared to be confirmed at laparotomy in three. Pathological examination is diagnostic and the condition appears to be always unilateral. Nephrectomy is curative.

Xanthogranulomatous pyelonephritis (XPN) is a rare outcome of bacterial infection of the kidney, characterised by unilateral destruction of renal parenchyma and the accumulation of lipid-laden foamy macrophages either surrounding abscess cavities or as discrete yellow nodules. Most cases have been described in women, generally they have a non-functioning kidney, urothelial changes, and urinary infection especially with Proteus species. The similarity of XPN to renal cell carcinoma has often been noted and the condition may also mimic perinephric abscess, pyelonephritis with stones, renal carbuncle, and tuberculosis.

Some 45 cases of XPN have been documented since the first description in 1963.5–4 We describe 5 more cases in order to stress the importance of considering XPN in the differential diagnosis of renal tumours.

Patients

Case 1. A 2-year-old boy was noticed at routine examination to be anaemic with weight below the 3rd centile and height on the 10th centile. A left-sided abdominal mass was palpable and an intravenous urogram (IVU) showed patchy calcification in the lower portion of the left kidney with irregular distortion and enlargement of the upper calyces. His haemoglobin concentration was 6·8 g/dl with a white cell count of 13·8 × 10⁹/l, 72% neutrophils. Urine analysis showed pyuria but no growth on culture.

After blood transfusion laparotomy was performed for a suspected Wilms’s tumour. This appeared to be confirmed at the time of operation with enlarged glands in the para-aortic and inferior mesenteric areas. Left nephrectomy and extensive lymph node dissection was performed. Vincristine 0·7 mg was given intravenously at the end of the operation.

Histological examination of the nephrectomy specimen showed changes typical of XPN with abscesses, lipid-filled histiocytes, and chronic inflammatory cells. Proteus sp. were obtained on culture of the pus. The lymph nodes showed reactive hyperplasia. He remains well and free of urinary infection 4 years later with a weight on the 25th centile and height on the 10th centile.

Case 2. A 3½-year-old boy was admitted for investigation of small stature, anaemia, and poor appetite. His weight was below the 3rd centile and his height between the 3rd and 10th centiles. Abdominal examination showed a palpable right kidney. His haemoglobin concentration was 8·5 g/dl with a white cell count of 19·8 × 10⁹/l. Urine analysis showed pyuria with no growth on culture. Calcification was noted in the right renal area on plain abdominal x-ray film and an IVU showed deformity of the right calyceal system in a kidney which was enlarged. Cystoscopy and cystogram showed no ureteric reflux. Operation for suspected pyelonephritis with stones was carried out. A large tumour mass was found which was adherent to the colon, duodenum, liver, and diaphragm with enlarged adjacent lymph nodes. Nephrectomy was performed and he was given vincristine 0·75 mg intravenously in theatre. Pathological examination
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