

# Fat-laden macrophages in cerebrospinal fluid as an indication of brain damage in children

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**SYNOPSIS** A study of the incidence of fat-laden cells (compound granular corpuscles) in the cerebrospinal fluid in infants indicating that a high level of these cells (over 40% of cells) is invariably associated with a bad prognosis and lower levels of these cells can give a useful indication of brain damage in children with meningitis and ventriculitis.

The presence of foamy cells in areas of degenerating brain has long been known (Virchow, 1867). In 1903 Nissl referred to them as 'Gitterzellen' or 'lattice cells', a name which had been suggested by his co-workers from their structure. Hortege (1919) suggested that they were phagocytic microglia and recent work using electron microscopy tends to confirm this hypothesis (Mori and Leblond, 1969) though the question is still debatable. In routine paraffin sections they vary in appearance either as small cells with a vacuole and flattened nucleus, or as large, rounded cells with cytoplasm stuffed with lipid or debris when they are usually called 'compound granular corpuscles'. The occurrence of these cells is not specific (Greenfield and Carmichael, 1925).

There are fine globules of fat in the brains of a high proportion of young infants at necropsy (Tuthill, 1938) and it has been shown that this fat, together with the presence of phagocytic cells, is considerably increased in brains undergoing experimental hydrocephalus (Weller, Wisniewski, Ishii, Shulman, and Terry, 1969). Such compound granular corpuscles can be found 24 hours after traumatic brain injury in adults (Nevin, 1967) and somewhat similar changes have been shown to occur experimentally in newborn rats (Sumi and Hager, 1968).

Studies on the phagocytic macrophages (microglia) in traumatic necrotic tissue in the rat have demonstrated that the material in the cytoplasm of these cells has a lamellar pattern with a 130 Å periodicity and distinct interperiod lines similar to that of myelinated axon (Uchino and Nakamura, 1964).

In cerebrospinal fluid two types of fat-laden cells occur—polymorphonuclear cells which pick up small fat droplets when there is an inflammatory reaction, and the more typical compound granular

corpuscles (Fig. 1). These are large cells, usually with a single compound nucleus and the cytoplasm has many large vacuoles, many but not all, of which stain for neutral fat. These cells gain entry to the cerebrospinal fluid where the ependyma is split, damaged or completely absent and can be identified in wet preparations as large cells with refractile points and an irregular outline (Fig. 2).

The purpose of this investigation was to determine whether the presence of these cells in cerebrospinal fluid might be an indication of the extent and progress of brain degeneration in children.

## Material and Methods

Over a period of one year (September 1969–August 1970), all the specimens of cerebrospinal fluid cultured in the laboratories of the Sheffield Children's Hospital were examined for the presence of fat-containing cells. Eight hundred and sixty-seven specimens were examined from 288 patients. The cell count of the cerebrospinal fluid was done in the usual way using a Fuchs-Rosenthal counting-chamber with the undiluted cerebrospinal fluid stained using 0.1% aqueous toluidine blue. The result was expressed in cells per cmm. Films of the centrifuged deposit were air dried, fixed in formalin vapour, and stained with Scharlach R, then lightly counterstained with haematoxylin. A differential count was done on the stained film giving the proportion of polymorphonuclear cells, lymphocytes, and fat-containing cells, and the results were expressed in percentages.

Most of the children studied had hydrocephalus associated with meningocele but the series covered a wide range of conditions including bacterial and viral meningitis, physical injury, leukaemia, tumours, vascular accidents, and primary hydro-

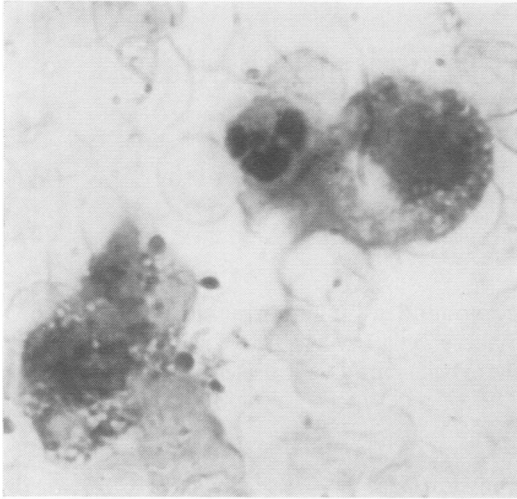


Fig. 1a

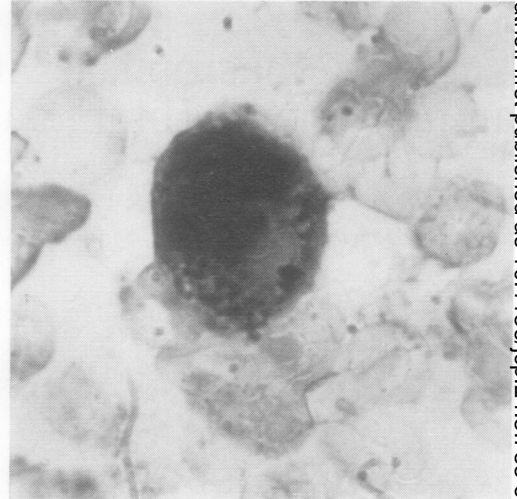


Fig. 1b

Fig. 1 Photograph of iodine vapour-fixed smear of cerebrospinal fluid stained with Sudan 4. The photograph shows erythrocytes, a polymorphonuclear cell with a single fat globule, and three compound granular corpuscles ( $\times 1,500$ ).

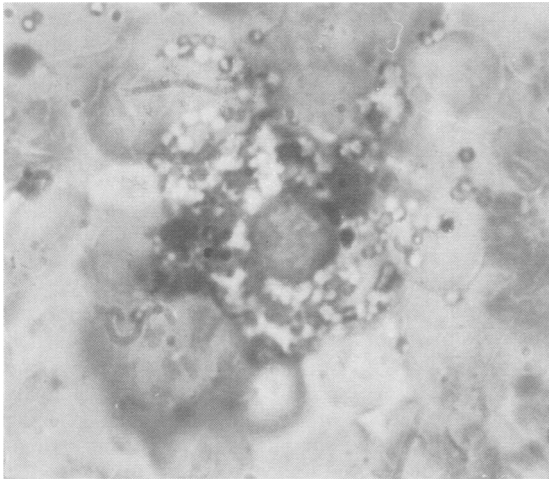


Fig. 2 Preparation similar to that seen in Figure 1 showing highly refractile fat globules in a compound granular corpuscle ( $\times 1,500$ ).

cephalus. The case notes were scrutinized through the courtesy of the clinicians. The pattern of histories varied greatly and these were put into three groups:

#### GOOD

Children who apparently completely recovered

clinically from the cerebral symptoms and were discharged or reported completely cured, ie, with apparent brain damage (35 cases).

#### BAD

Children who had obvious progressive brain damage leaving them either grossly defective or who died and came to necropsy (16 cases).

#### INTERMEDIATE

Children having changing cerebral symptoms and who fitted into neither category above (28 cases).

These categories were studied in relation to the numbers of compound granular corpuscles seen in the cerebrospinal fluid samples.

#### Results

Of the 867 specimens of cerebrospinal fluid examined 335 (approximately one third) were positive. These came from 94 of the 288 children studied. Of 200 consecutive positive specimens analysed 79 had up to 5% compound granular corpuscles, 23 had 6-10%, 37 had 11-20%, 18 had 21-30%, 27 had 21-50%, and 16 had over 50% compound granular corpuscles.

When we analysed the percentage of fat cells related to the pattern of clinical histories above into three groups, we found that almost all of the cases having a good clinical prognosis showed less than 10% compound granular corpuscles, those with a

bad prognosis had more than 30%, and the intermediate group showed intermediate levels. Illustrative cases of the three groups are as follows.

**GROUP 1: LESS THAN 10% COMPOUND GRANULAR CORPUSCLES**

These children were usually those in whom only occasional specimens of cerebrospinal fluid showed the presence of fat cells and then only in small numbers. Nearly all of these children recovered with no apparent brain damage. They included children with viral meningitis, bacterial meningitis, and leukaemia with cerebral involvement.

*Case 1: a child with meningococcal meningitis*

On admission the first cerebrospinal fluid showed approximately 10,000 polymorphs and meningococci but no fat cells were seen.

Treatment was commenced immediately but three days later he had a generalized convulsion with a high temperature. Cerebrospinal fluid at that time showed 3% fat cells. One week later another cerebrospinal fluid showed 250 WBCs with 2% fat cells. A subdural effusion was considered as the cells seemed to be taking a little time to go but an ultrasound scan of the skull did not suggest the presence of any collection of this kind.

A further cerebrospinal fluid count done about 10 days later showed only 46 cells were present and no fat cells. The child was discharged home on no treatment and on follow up there were no neurological signs. The child probably had a small venous thrombosis at the time of the convulsion.

*Case 2: a child with tuberculous meningitis*

Admitted at the age of 29 months, the cerebrospinal fluids were consistently negative for compound granular corpuscles in the initial period and while she was on antituberculin therapy; approximately two dozen specimens were examined over this period. She made considerable clinical improvement and intrathecal therapy was stopped but after about one month she deteriorated, when the intracranial pressure was found to be raised and hydrocephalus developing. At this time the cerebrospinal fluids became fat positive (2%). A Holter valve was inserted, the pressure dropped and, within three days, the cerebrospinal fluids were fat negative again and have remained so. She improved, was able to go home; her speech is now good, she hears well, and has no headache or vomiting.

The period of positive compound granular corpuscles in this child was associated with a rise in cerebrospinal fluid pressure and hydrocephalus, all of which were relieved when the latter was treated by insertion of a valve.

**GROUP 2: 30% OR MORE COMPOUND GRANULAR CORPUSCLES**

*Case 3: a child with a massive cerebral necrosis*

This boy first presented aged 3½ months with running eyes and cough, followed by a chest infection and diarrhoea. He was severely ill for a short time and later it was noted that his legs appeared spastic. He was finally admitted at 5 months because of a suspicion of fits.

Ventricular tap showed xanthochromic fluid at 150 mm pressure. There were 9 WBCs per cmm, the protein was >0.1 g%, and the compound granular corpuscle preparation showed that 45% of the cells contained fat. Ventricular taps were carried out periodically; sometimes both ventricles required tapping in order to deflate the opposite side. Approximately 15-20 ml of fluid was removed from each ventricle almost every day, but on the days before death there appeared to be a build-up in pressure with a removal of 50 ml on the day of death. The level of fat-positive cells was then 75%.

At necropsy there was extensive necrosis of the white matter of the frontal lobes extending back through both hemispheres. Histology of the brain showed degenerative tissue with a large number of compound granular corpuscles. There was no evidence of longstanding basal meningitis and it seemed most likely that the massive cerebral necrosis had followed a vascular catastrophe with gross cerebral ischaemia at the time of the acute illness six weeks before death.

**GROUP 3: FAT-POSITIVE CEREBROSPINAL FLUIDS OF INTERMEDIATE LEVEL BETWEEN 10 AND 30%**

*Case 4: a child with meningomyelocele and hydrocephalus*

This boy with spina bifida and hydrocephalus was admitted at birth. He developed ventriculitis associated with *Strep. viridans* throughout which time the cerebrospinal fluids were fat positive at around 20%. Eventually the infection cleared but there still remained a few cells in the cerebrospinal fluid of which less than 10% were fat positive. He needed a valve for increased head circumference but as the cerebrospinal fluid had a high protein level it was thought inadvisable to insert one. For a few weeks the child's condition stabilized and the specimens became fat negative but later the cerebrospinal fluid pressure rose rapidly and the insertion of a valve was essential. The cerebrospinal fluid taken at the time of valve insertion showed 22% fat cells.

The child, now at 10 months, although alive, remains in poor condition and we feel that the

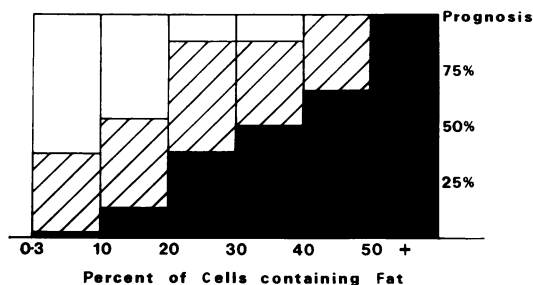


Fig. 3 The relationship of the proportion of nucleated cells in cerebrospinal fluid containing fat globules to the prognosis of the child. The solid black areas indicate either the death of the child or severe mental degeneration. The clear areas indicate apparent complete recovery of the child, and the hatched areas, children with continuing symptoms.

prognosis for this child is not good. In this child the first ventriculitis was associated with compound granular corpuscles in the cerebrospinal fluid possibly suggesting that the brain necrosis had preceded the streptococcal infection. The later rise in compound granular corpuscles could well have been a consequence of brain damage secondary to the acute intracranial pressure.

When the prognosis of the children in the clinical groups—good, bad, intermediate—was related to the level of fat cells, it was found that all the children with over 50% of the cells containing fat died. Above 30% the proportion of ‘bads’ was still high and very few children showed complete recovery. It is not until the number of fat cells is below 20% that half of the children show complete recovery (see Fig. 3).

## Conclusion

The value of the study of compound granular corpuscles seems, to us, to lie in two fields: first, there appears to be a direct relationship between the occurrence of a high level of compound granular corpuscles and a bad prognosis. Secondly, a sudden appearance of fat cells at a low level may indicate a rise in cerebrospinal fluid pressure, a small area of brain damage which may precede a phase of intracranial hypertension, or a ventriculitis.

We feel that the enumeration of these cells in our own cases is a simple and worthwhile procedure and merits addition to the routine study of cerebrospinal fluid in children.

We wish to acknowledge the courtesy of the paediatricians at the Sheffield Children's Hospital for access to the case records of the children studied. Photomicrographs by Mr A. Tunstill.

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