gradient and $Paco_2$ levels generally within normal limits, and suggested that this defect was mostly due to intrapulmonary venous admixture. In adults with unilateral relaxation of the diaphragm and without associated pulmonary disease, Poppius, Varpela, and Korhonen (1969) found slightly increased dead-space ventilation and venous admixture, but no signs of asynchronous ventilation; however, one patient with bilateral involvement had abnormally low Pao_2 and high $Paco_2$ levels, with dyspnoea at rest.

In Case 1, though other causes of increased central venous pressure could not be excluded, the high pressure in the right atrium suggested that intrapleural pressure was close to zero. This, and the marked decrease of lung expansion and transparency on chest film, indicated that lung volumes were much decreased and well below the 'closing volume' (Mansell, Bryan, and Levison, 1972) of several peripheral lung units, explaining the large alveolar-arterial Po_2 gradient during high oxygen breathing. In both patients, breathing with a CPAP of 5 to 7 cm H_2O presumably restored a transpulmonary pressure gradient high enough to reopen part of these units.

Early neonatal death has occurred not uncommonly in phrenic nerve palsy, being usually attributed to pneumonia (Richard *et al.*, 1957). However, in some patients dying in the early days of life (Keuth, 1971), as well as in one dying at the age of 47 days (France, 1954), massive atelectasis was the only postmortem finding, suggesting that lung collapse *per se* may cause death in some cases. Mechanical ventilation has been proposed in the treatment of early pulmonary failure in neonatal phrenic nerve palsy (Keuth, 1971). However, the present study indicates that, provided that a sufficient lung volume is maintained by the administration of transpulmonary pressure, spontaneous ventilation by still functioning respiratory muscles is adequate. CPAP breathing by nasal cannula appears to be a simple and effective way to manage these patients. It may allow spontaneous recovery of diaphragmatic function in some cases, or postponement of surgical plication of the diaphragm in others.

Summary

Two newborn infants with respiratory failure due to phrenic nerve palsy were treated with continuous positive pressure breathing applied by nasal cannula. Rapid improvement of clinical, *x*-ray, and arterial oxygen findings followed. Some weeks after suspension of the treatment, respiratory symptoms had disappeared in one patient, but persisted to a moderate degree in the other.

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REFERENCES

Caliumi-Pellegrini, G., Agostino, R., Orzalesi, M., Nodari, S., Marzetti, G., Savignoni, P. G., and Bucci, G. (1974). Twin nasal cannula for administration of continuous positive airway pressure to newborn infants. *Archives of Disease in Childhood*, **49**, 228.

France, N. E. (1954). Unilateral diaphragmatic paralysis and Erb's palsy in the newborn. *Archives of Disease in Childhood*, **29**, 357.

Keuth, U. (1971). *Handbuch der Kinderheilkunde*, Vol. 1, Part 2, p. 128. Ed. by H. Opitz and F. Schmid. Springer, Berlin.

Mansell, A., Bryan, C., and Levison, H. (1972). Airway closure in children. *Journal of Applied Physiology*, **33**, 711.

Murdock, A. I., Burrington, J. B., and Swyer, P. R. (1971). Alveolar to arterial oxygen tension difference and venous admixture in newly born infants with congenital diaphragmatic herniation through the foramen of Bochdalec. *Biology of the Neonate*, **17**, 161.

Nodari, S., Agostino, R., and Bucci, G. (1973). Proper location of umbilical venous catheters by internal electrocardioscopy. *Acta Paediatrica Scandinavica*. **62**, 492.

Orzalesi, M. M., Mendicini, M., Bucci, G., Scalamandrè, A., and Savignoni, P. G. (1967). Arterial oxygen studies in premature newborns with and without mild respiratory disorders. *Archives of Disease in Childhood*, **42**, 174.

Poppius, H., Varpela, E., and Korhonen, O. (1969). Respiratory function and exercise tolerance in relaxation of the diaphragm. *Scandinavian Journal of Respiratory Diseases*, **50**, 68.

Richard, J., Chevalier, V., Cappelle, R., Cavrot, E., Content, J., and Delforge, J. (1957). La paralysis diaphragmatique obstétricale. A propos de dix cas. *Archives Françaises de Pédiatrie*, **14**, 563.

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Krabbe's globoid cell leucodystrophy with hydrocephalus

Globoid cell leucodystrophy (GLD) is a rapidly fatal, hereditary neurological disorder of infants. Since Krabbe's first description in 1916, less than 100 cases have been reported. Mostly the reports have concerned single cases or a few sibs, with one noticeable exception (Hagberg *et al.*, 1969).

Recently, specific enzyme deficiencies have been shown in various tissues (Andrews *et al.*, 1971; Austin *et al.*, 1970; Miyatake and Suzuki, 1972; Suzuki, Schneider, and Epstein, 1971; Suzuki and Suzuki, 1971) making a diagnosis possible before death by an assay of peripheral leucocytes from a patient, or even amniocytes from a fetus at risk.

This is a report of a case of GLD associated with hydrocephalus.

Case report

The patient was a girl, born in October 1971 to unrelated parents. There was no history of GLD in the family. From the beginning the patient was irritable and was never noticed to smile.

Physical examination at 3 months showed intermittent circulatory eye movements and poor pupillary light response. 2 weeks later intermittent opisthotonus and increasing feeding difficulties were noticed. CSF was under normal pressure, without pleocytosis, but with raised protein of 125 mg/100 ml.

At 4 months nystagmoid eye movements and myoclonic jerks of the lower extremities started. CSF protein was now 250 mg/100 ml with albumin fraction 90% of the total. The clinical diagnosis of GLD was proposed.

At 5 months the child was out of contact with the environment, with unobtainable deep tendon reflexes, unresponsive pupils, and had to be fed by gavage. There was slight temporal pallor of the optic discs. The head circumference was in the 50th centile (42·5 cm) with normal fontanelle tension. A skull *x*-ray was normal, but a pneumoencephalogram (PEG) showed a marked dilatation of the lateral and 3rd ventricles, the latter measuring 25 mm in diameter. The aqueduct was also widened, measuring 7 mm. The 4th ventricle looked normal. No air could be obtained over the cortex, but there was a considerable air collection in the basal cisterns.

Over the next 2 weeks, the head circumference increased by 2 cm with a bulging fontanelle and a right abducens palsy. A subdural tap was negative. A ventriculo-peritoneal shunt of Ames type was performed. After operation the child responded better and the abducens palsy improved temporarily. The body temperature remained unstable.

Five weeks after the shunting, a PEG showed a further increase of 4 mm in the diameter of the 3rd ventricle, but the 4th ventricle remained normal. As before, no air went up across the hemispheres. The head circumference remained at the 90th centile after the shunt procedure.

Frozen leucocytes were sent to the University of Calgary and an enzyme assay showed a conspicuously decreased activity of galactocerebroside β-galactosidase (Table).

Death occurred at age 11 months.

TABLE

Galactocerebroside β-galactosidase activities in leucocytes, brain, and liver from the affected child and in leucocytes from the parents (nmol substrate hydrolyzed/mg protein per hr)

	Affected child	Mother	Father
Leucocytes	0·29, 0·38 (2·94)	2·40 (2·48)	1·16 (2·48)
Brain	<0·01 (1·65)		
Liver	<0·01 (0·48)		

Note: Controls in parentheses.

Necropsy findings. The dura was slightly thickened with traces of old postoperative subdural blood. The brain weighed 670 g after formalin fixation. Before fixation fresh tissue was sampled for enzyme assay, which was found to be low (Table). On external inspection there was a proportional reduction in the size of the cerebellum and both temporal lobes were greatly thinned medially, with the appearance of fluid-filled cysts. Adhesions were not seen around the base or near the foramina of the 4th ventricle. Serial sections (Fig. 1) revealed considerable dilatation of the ventricular system, except for the 4th ventricle, which was of normal size and into which the aqueduct opened freely. The greatest expansion was that of the temporal horns. The cerebral and cerebellar white matter was reduced, grey-brown, and firm. Longitudinal cystic cavities were noted externally along both lateral ventricles. The cortex was grossly normal, except in the temporal lobes, where it could no longer be distinguished due to the extreme atrophy of the brain tissue.

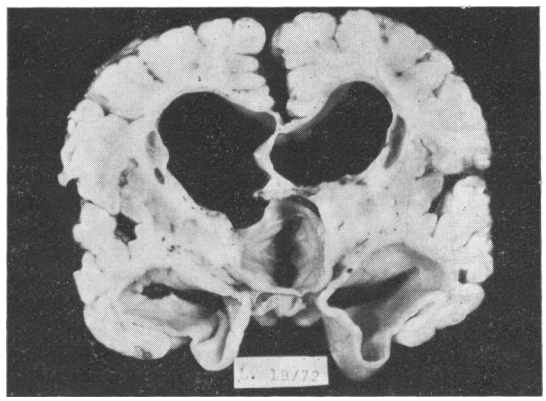

FIG. 1.—*Section of the brain showing ventricular dilatation. Note thinning of temporal lobes.*

Microscopical examination of the cerebrum, cerebellum, brain stem, spinal cord, and optic nerves revealed extensive demyelination, gliosis, and globoid cells in the white matter, typical for GLD (Fig. 2). The cranial and spinal leptomeninges were slightly but diffusely thickened, with a mild chronic inflammatory reaction. A thin layer of newly formed connective tissue lined the dura.

Focal demyelination and round cell infiltration with axonal degeneration were noted in the medullary and spinal nerve roots. Sections of peripheral nerves (brachial plexus and femoral nerve) revealed severe degeneration of myelin sheaths and axons, as described by Sourander (Sourander and Olsson, 1968).

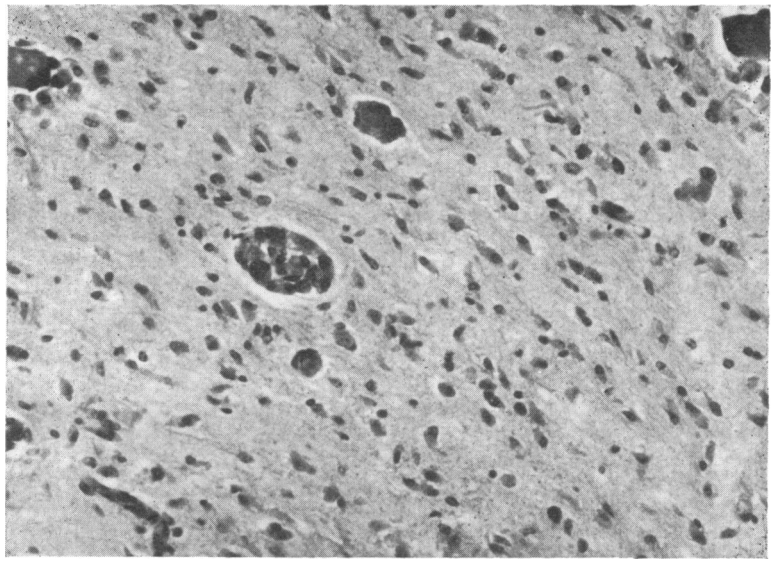

FIG. 2.—*Photomicrograph of the cerebral white matter, showing typical globoid cells, both scattered and grouped around blood vessels. Giant cells are present.* (*H. and E.* ×602.)

Discussion

A mild enlargement of the ventricular system, secondary to the reduction of the white matter, may accompany GLD, but there is no mention of frank hydrocephalus in the published reports. Hydrocephalus of the degree found in the present case can hardly be explained by atrophy only. The ventricular dilatation found before the clinical signs of hydrocephalus, the continued expansion of the 3rd ventricle after the shunting, and the normal size of the 4th ventricle can all be explained by the progressive cerebral destruction of GLD, but an added obstructive element is suggested by the temporary rise in CSF pressure and the enlarging head size, which was relieved by the ventriculo-peritoneal shunt. The extreme thinning of the temporal lobes also points to a rise in CSF pressure, though some other unrelated factors might have played a part, such as symmetrical porencephaly, selectively affecting the temporal lobes (Blackwood *et al.*, 1963).

It is of interest that clinical signs of hydrocephalus were first noticed shortly after the PEG, which indicates that the procedure itself might in some way have upset the balance of CSF flow, possibly through the mild leptomeningial irritation found here. To our knowledge leptomeningitis is not a feature of the pathological picture of GLD.

Whatever the cause may be, we call attention to the potential development of hydrocephalus in a child with GLD, with a consequent aberrant clinical course.

Summary

Hydrocephalus of an unusual degree was found in association with Krabbe's globoid cell leucodystrophy, causing diagnostic difficulties.

We are greatly indebted to Dr. J. T. R. Clarke, University of Calgary, Canada, for performing the enzyme assays.

REFERENCES

Andrews, J. M., Cancilla, P. A., Grippo, J., and Menkes, J. H. (1971). Globoid cell leukodystrophy (Krabbe's disease). Morphological and biochemical studies. *Neurology*, **21**, 337.

Austin, J., Suzuki, K., Armstrong, D., Brady, R., Bachhawat, B. K., Schlenker, J., and Stumpf, D. (1970). Studies in globoid (Krabbe) leukodystrophy (GLD). V. Controlled enzymic studies in ten human cases. *Archives of Neurology*, **23**, 502.

Blackwood, W., McMenemey, W. H., Meyer, A., Norman, R. M., and Russel, D. S. (Editors) (1963). *Greenfield's Neuropathology*, 2nd ed., p. 353. Williams and Wilkins, Baltimore; Arnold, London.

Hagberg, B., Kollberg, H., Sourander, P., and Åkesson, H. O. (1969). Infantile globoid cell leucodystrophy (Krabbe's disease). A clinical and genetic study of 32 Swedish cases 1953–1967. *Neuropädiatrie*, **1**, 74.

Miyatake, T., and Suzuki, K. (1972). Globoid cell leukodystrophy; additional deficiency of psychosine galactosidase. *Biochemical and Biophysical Research Communications*, **48**, 539.

Sourander, P., and Olsson, Y. (1968). Peripheral neuropathy in globoid cell leucodystrophy (morbus Krabbe). *Acta Neuropathologica*, **11**, 69.

Suzuki, K., Schneider, E. L., and Epstein, C. J. (1971). *In utero* diagnosis of globoid cell leukodystrophy (Krabbe's disease). *Biochemical and Biophysical Research Communications*, **45**, 1363.

Suzuki, Y., and Suzuki, K. (1971). Krabbe's globoid cell leukodystrophy; deficiency of galactocerebrosidase in serum, leukocytes and fibroblasts. *Science*, **171**, 73.

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The 'grey toddler'

Chloramphenicol toxicity

Reports of neonatal death associated with the administration of chloramphenicol first appeared in 1959 (Sutherland, 1959; Lischner *et al.*, 1961). In most cases therapy had been instituted in the first 2 days of life and symptoms became apparent 36 to 48 hours later. The characteristic features were abdominal distension, vomiting, progressive pallid cyanosis, irregular respiration, hypothermia, and vasomotor collapse (the 'grey baby' syndrome). Death followed if treatment was continued, but rapid and complete recovery usually took place if chloramphenicol therapy was terminated. The babies had high serum chloramphenicol concentrations because of slow glucuronide conjugation within the immature liver (Weiss, Glazko, and Weston, 1960).

The toxic effects of chloramphenicol have not been described in children more than 2 months old. We therefore describe a child of 25 months with features characteristic of the 'grey baby' syndrome and a high blood chloramphenicol level, and 2 younger children with similar symptoms in whom estimates of blood chloramphenicol concentrations were not obtained.

Case reports

Case 1. A 25-month-old boy was admitted to hospital in September 1972 with a 7-hour history of progressive pallor and withdrawal. Examination revealed a sick child who had a good peripheral circulation and normal blood pressure. Rectal temperature was 38·7 °C and there was moderate neck stiffness. Lumbar puncture produced a cloudy fluid with 5000 polymorphs/mm^3, protein 472 mg/100 ml, and glucose less than 10 mg/100 ml. A Gram stain showed pleomorphic Gram-negative bacilli in the film; a diagnosis of *Haemophilus influenzae* meningitis was made and later confirmed by culture. Intravenous treatment was started with sulphadimidine 150 mg/kg per day and chloramphenicol sodium succinate 110 mg/kg per day, together with 250 mg streptomycin twice a day intramuscularly. The child was much improved, taking notice of his surroundings, and was apyrexial within 18 hours.

Then, 36 hours after treatment was started, he vomited a small amount of bile-stained fluid, the abdomen became slightly distended, and bowel sounds became sparse. Intravenous fluids were continued and he was treated with nasogastric suction, but after 68 hours he rapidly worsened with a grossly distended abdomen, absent bowel sounds, deep sighing respiration, and an ashen-grey appearance. A severe metabolic acidosis (*p*H 7·23, base excess −14) was partially corrected with sodium bicarbonate and plasma was later given for peripheral circulatory collapse. At 71 hours he had a cardiac and respiratory arrest but received immediate cardiac massage and responded after 14 minutes.

The possibility of this very unusual picture being due to chloramphenicol toxicity was suggested by Professor J. K. G. Webb and treatment with this drug was therefore discontinued. Within 12 hours of substituting ampicillin for chloramphenicol the abdomen was softer, and within 24 hours there were bowel sounds and other signs of general improvement. The blood chloramphenicol concentration was measured during the period of recovery using a microbiological assay (adapted from the method described by Grove and Randall, 1955) and a biochemical assay (Kakemi, Arita, and Ohashi, 1962), the results being summarized in the Fig. Serum

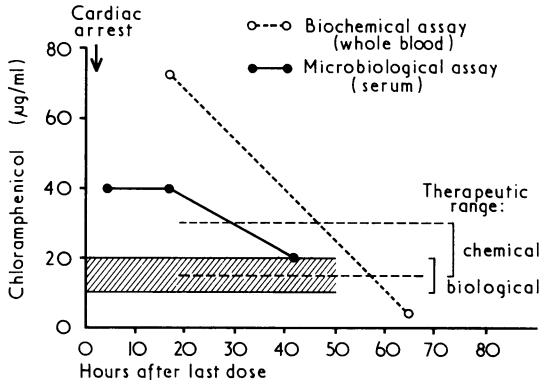

FIG.—*Chloramphenicol concentrations as determined by microbiological assay of serum and a biochemical method of whole blood. (The difference in the results from the two assays is due to the high affinity of red cells for chloramphenicol.)*

bilirubin was 0·7 mg/100 ml and serum glutamic oxaloacetic transaminase 70 IU/l. shortly after cardiac arrest; 48 hours later these had risen to 3·0 mg/100 ml and 163 IU/l., respectively, but they returned to normal over the next 7 days.

The boy later developed severe pneumonia and diarrhoea with monilial overgrowth of the bowel, but made a complete mental and physical recovery and was discharged home after a total of 3 weeks in hospital. The parents are unwilling to countenance further liver function studies at present but they feel he is none the worse for his experience.