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Case reports

Congenital Varicella-Zoster

A serologically proven case with necrotizing encephalitis and malformation

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Summary. Following maternal chicken pox in the 14th week of pregnancy, a male infant was born with low birth weight, muscle wasting and limb contractures, hypotonia and areflexia. A rising titre of varicella-zoster-specific IgM (by enzyme-linked immunoabsorbent assay) confirmed congenital infection, and electromyogram showed widespread denervation. Death occurred at 8 days. Neuropathological examination revealed destructive and inflammatory lesions of cerebral cortex and white matter, thalamus, brain stem and spinal cord. In addition there were cerebellar heterotopias and bilateral polymicrogyric malformations of the insular cortex.

Key words: Varicella-zoster – Congenital infection – Encephalitis – Malformation – Polymicrogyria

Fetal and neonatal varicella-zoster (V-Z) infection is comparatively rare: maternal infection is usually acquired during childhood and there is passive antibody transfer across the placenta. When primary maternal infection occurs during pregnancy – 0.7 per 1000 pregnancies in one large US study [24] – the outcome for the infant depends on the period of gestation when infection takes place. A V-Z infection in the last trimester may occasionally give rise to a typical varicella illness or a fatal disseminated infection in the neonatal period. A much rarer phenomenon is the occurrence of multiple congenital defects following maternal V-Z complicating the first or second trimester. There have been occasional clinical case reports of congenital V-Z embryopathy and a review [10], but despite the high mortality only one full pathological study [25]. We report here a new case with serological confirmation of intra-uterine infection and both clinical and pathological evidence of severe neurological involvement including both necrotic and encephalitic lesions and an associated CNS malformation.

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Case report

A male infant was the second child of healthy non-consanguinous Caucasian parents; their first child, a girl, was entirely well. Mother had a clinical episode of chickenpox in the 14th week of pregnancy for which she was attended by her family physician. Ultrasound scan at 17 weeks was normal with a normal volume of liquor and a bi-parietal diameter of 3.9 cm confirming the dates. Pregnancy continued uneventfully and she was admitted in established labour at 37 weeks 5 days. The baby presented as a footling breech and developed fetal distress with meconium stained liquor and a tachycardia of 180/min. Delivery was therefore expedited by emergency caesarian section. The baby was asphyxiated at birth, Apgar scores were 2 and 6 at 1 and 5 min respectively, and required intubation with intermittent positive pressure ventilation for 5 min. Birth weight was 2.11 kg, less than the 3rd centile for gestation; head circumference was 32 cm. Initial examination revealed a wasted infant with stridor and marked postural deformities: flexion contractures of the left elbow, right wrist and fingers, both hips and knees, and bilateral talipes equinovarus. The upper limbs were hypotonic, and tendon reflexes absent, but there were good facial movements. There appeared to be a pressure sore over the dorsum of the right foot. The baby was intubated and electively ventilated because of upper airways obstruction, and the right foot was strapped.

Full blood count, urea, electrolytes and plasma proteins were normal and the baby showed normal male karyotype. At 4 days of age neurophysiological studies were undertaken. EMG showed profuse denervation, mainly fibrillation, potentials from all muscles tested except facial muscles. Attempted stimulation of the lateral popliteal nerve at the head of the fibula, and peripheral nerves at Erb's point in the right upper limb, produced no clinical or electrical response. However, high threshold stimulation of the facial nerve in front of the pinna induced some facial twitching. At 48 h post-partum the baby was breathing adequately without ventilation but continued to need an endotracheal tube to prevent severe stridor. Gradual deterioration occurred over the next few days and he died on the 8th day.

Complement fixation titres for cytomegalovirus and herpes simplex were less than 1 in 10, measles titre was 1 in 10, and

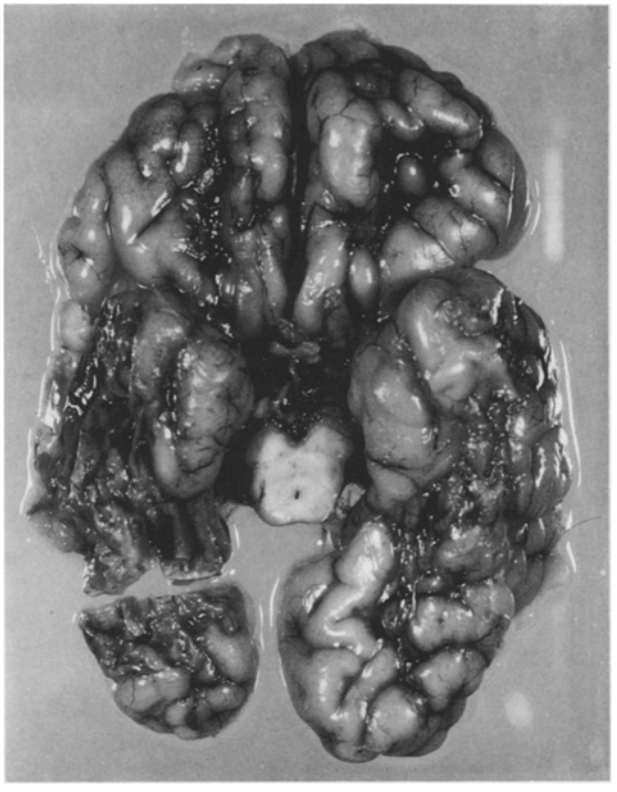

Fig. 1. Base of the brain showing bilateral scarring of orbital cortex, and extending over temporal and occipital lobes as shrunken narrow gyri

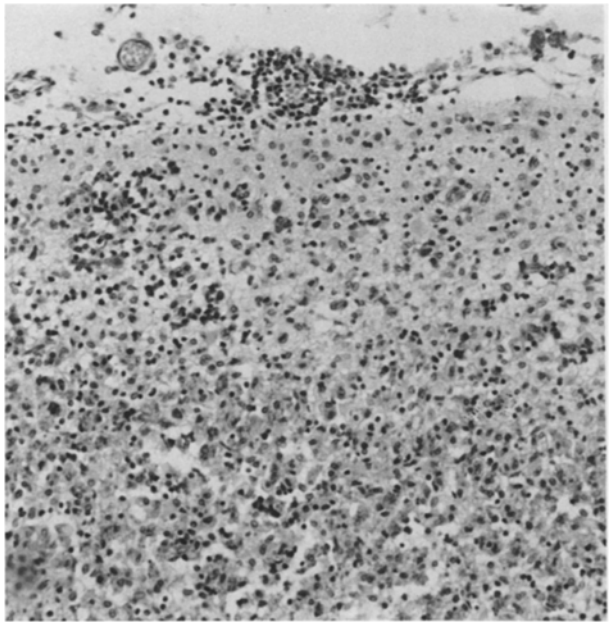

Fig. 2. Photomicrograph from an area of cortical necrosis showing inflammatory infiltration of the leptomeninges and complete replacement of the cortical ribbon by inflammatory and granulation tissue including many mononuclear cells and foamy macrophages. Haematoxylin and eosin, × 156

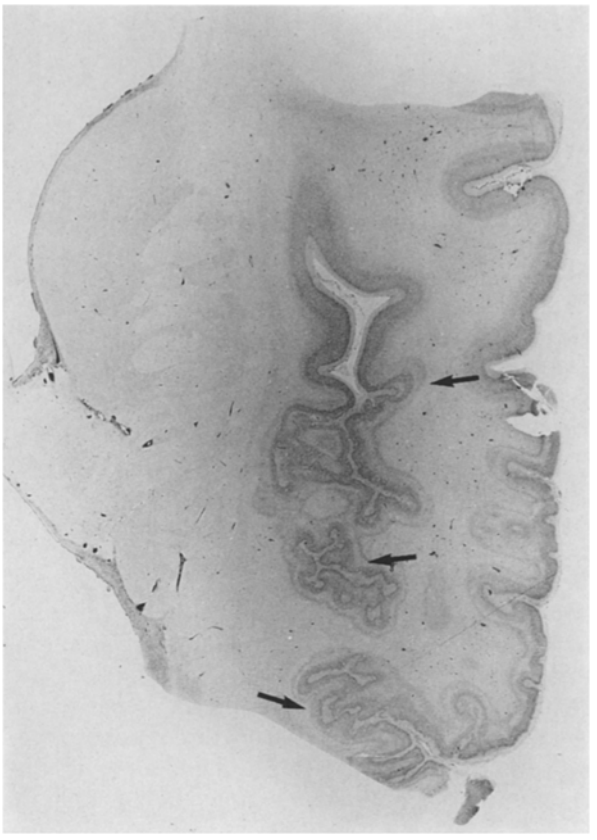

Fig. 3. Low-power photomicrograph of a horizontal section through basal ganglia and insula. Compare the irregular pseudoglandular arrangement of the partially buried mini-convolutions of four-layered cortex in the polymicrogyric areas (*arrows*) with adjacent normal cortex. Luxol fast blue – cresyl violet, × 3.3

toxoplasma screening test was negative. V-Z titres for mother and baby are shown in Table 1. A significant level of V-Z-specific IgM was detected with the enzyme-linked immunosorbent assay (ELISA), although prior examination with the immunofluorescence (IF) technique was negative.

No virus was isolated from cultured post-mortem samples of brain, liver, lung, kidney, spleen, cardiac and skeletal muscle and naso-pharyngeal aspirate.

Table 1. Varicella-Zoster serology

	Immunofluorescence		cap ELISA
	IgG	IgM	IgM test/control
Mother	1 in 512	ND	3.2
Baby, day 1	1 in 512	ND	3.8
Baby, day 6	1 in 512	ND	5.5

Control = 1; significant > 2 × control; ND = not detected

Post-mortem findings

General examination revealed severe restriction of joints with fixed dislocation of both hips, oedema and congestion of the

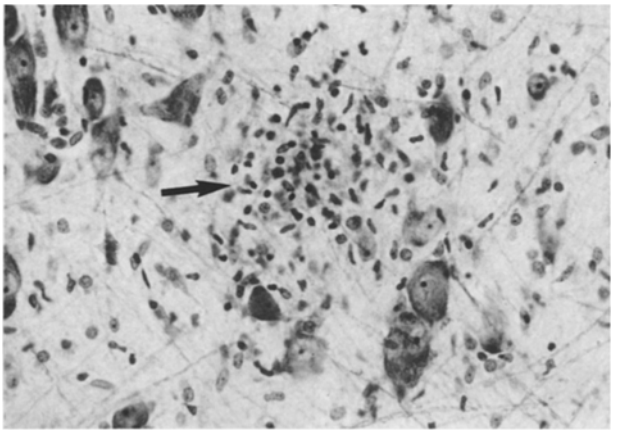

Fig. 4. Photomicrograph of the interpeduncular nucleus in the midbrain, showing a microglial nodule (*arrow*). Luxol fast blue – cresyl violet, ×248

lungs, and normal cardiovascular, gastrointestinal and genito-urinary systems.

Neuropathology

The fixed brain weighed 270 g (normal at 39 weeks gestation – 300 g), the brain stem and cerebellum accounting for 25 g. The convolutional pattern appeared normal. The optic nerves were small and grey. Linear yellow scars were present over the orbital frontal, temporal and occipital surfaces of both hemispheres (Fig. 1). On horizontal slicing the cortical ribbon showed numerous yellow necrotic lesions and multilocular cysts involving large areas of both hemispheres, but especially severe in temporal and occipital lobes and frontal poles.

On microscopical examination (Fig. 2), the necrotising cerebral lesions involved leptomeninges, the whole depth of the cortex and subjacent white matter, and comprised granulation tissue heavily infiltrated with chronic inflammatory cells, mononuclear cells, plasma cells and lymphocytes, larger histiocytic cells and lipid phagocytes, as well as hypertrophic astrocytes around the periphery of the lesions. There was considerable tissue breakdown with formation of rough-walled cysts crossed by glio-mesodermal bridges.

The insular cortex and adjacent parietal cortex (Fig. 3) in both hemispheres showed extensive polymicrogyric malformation with a pseudo-glandular arrangement of buried microgyri consisting of abnormally thin four-layered cortex. Scattered foci of necrosis were present in the microgyric areas.

In the thalamus there was patchy neuronal loss and gliosis, scattered chronic inflammatory cells, and perivascular cuffs of mononuclear and plasma cells. In the brain stem a small number of microglial nodules were found, but no definite neuronophagia or viral inclusions. Microglial nodules were present in the midbrain, middle cerebellar peduncle and olive (Fig. 4).

Cerebellar cortex and dentate nuclei appeared normal, but in the white matter of both cerebellar hemispheres were several quite large heterotopic collections of nerve cells, in one case organised into external and internal granular layers, Purkinje and molecular layers.

The spinal cord throughout was very small. At cervical levels anterior horns appeared well populated by neurons but the posterior horns and lateral columns were shrunken and gliotic. At lumbar level the cord was reduced to a thin plate of gliotic tissue possessing only small numbers of ferruginated neurons. The only dorsal root ganglion available for study, from a cervical segment, showed ganglion cell loss and formation of Nageotte nodules.

Discussion

Congenital V-Z embryopathy is rare. Since being first described by Laforet and Lynch [18], there have been a further 20 clinical case reports [1, 4–6, 8–14, 17, 19, 22, 23, 25, 26], 17 after maternal chickenpox, 3 following maternal zoster, and 1 after maternal zoster varicellosus. Serological confirmation of fetal infection has been obtained in most cases, but usually by demonstrating persistence of V-Z antibody (by complement fixation or fluorescent-antibody membrane-antigen test) beyond the age when maternal antibody should have disappeared. More convincing evidence of intrauterine infection, the presence of V-Z-specific IgM, has been more difficult to obtain. Only in two cases has this been achieved, by fractionation of the baby's serum on a sucrose density gradient [5, 13]. Our patient is the first with this condition, in whom V-Z-specific IgM has been detected by the ELISA method. The IF method for specific IgM was unsuccessful, as in a previous case [12].

Reported clinical manifestations in V-Z embryopathy include combined defects of the skin, musculoskeletal system, eye and brain [10]. Although the commonest constellation of findings is a hypoplastic limb with cicatricial scarring of the overlying skin [4, 8, 10, 12, 17–19, 22, 23, 25], there is a spectrum of abnormality ranging from severe multiple anomalies incompatible with life to milder involvement of just one eye [14]. The present case is slightly unusual in not exhibiting skin or eye problems, but in common with many other cases has severe brain involvement [9, 10, 13, 18, 19, 23, 25] and evidence of peripheral neuropathy and muscle denervation [1, 4, 8–10, 17–19, 22, 23, 25].

The zoster-like distribution of the cutaneous scarring, and the dermatomal distribution of the various anomalies, i.e., a unilateral hypoplastic limb, or thoracic or abdominal wall deficiency, suggests that maternal varicella had resulted in fetal zoster [10]. This view is supported by the development, in three cases of V-Z embryopathy, of fresh zoster lesions during infancy [4, 9, 17]. The involvement of the PNS in the pathogenesis of this syndrome is further underlined in the present case by electrophysiological evidence of denervation, as well as histological confirmation of spinal cord and dorsal root ganglion involvement, which has only been described once previously [25].

Nine of the 21 reported cases of V-Z embryopathy have died, but details of autopsies are scarce and neuropathological data rather scanty. In Alexander's

patient [1] there was pathological evidence of systemic infection but the brain convolutions were described as normal. In three other examples there was severe destruction of the brain. The first two {[10] (Case 7), [13]} mentioned the brain only briefly, but personal examination of the histological sections has confirmed the similarity of their morphological changes, cystic necrosis of the hemisphere, with those described in detail by Srabstein et al. [25]. These are non-specific end-stage lesions, which provide no definite clues to pathogenesis. In our case, also, there is widespread cerebral necrosis though the lesions are more discrete and less confluent. Moreover, the composition of the inflammatory infiltrate, including lymphocytes and plasma cells, and the presence of subcortical perivascular inflammatory cuffings and brain stem microglial nodules is rather more suggestive of an ongoing viral infection, despite the lack of specific viral inclusions.

The presence of cerebral malformations, as opposed to destructive lesions, has not been reported previously in V-Z embryopathy. Polymicrogyria is a relatively common malformation, which has been described in association with a number of different types of prenatal insult, including intrauterine infections. However, until now the only viral infection for which there has been consistent and convincing evidence is cytomegalic inclusion disease [3, 7].

The pathogenesis of polymicrogyria is still controversial, but there is evidence, both for some disturbance of neuroblast migration [15, 20] and a post-migratory selective laminar necrosis, of a possible hypoxic-ischaemic origin [21]. The arguments are based on cytological, histological (topographical) and clinical information regarding the timing of a possibly causative noxious insult. Two reports of polymicrogyria following maternal coal gas poisoning at or before 24 weeks gestational age [2, 16] are rare examples, where accurate timing of the insult can be made. While there is fairly precise information in our case regarding the timing of the maternal V-Z infection, and by implication the coincident materno-fetal viraemia, our histological and serological evidence indicates the continuation of infection throughout the gestational period.

In speculating on the possible pathogenetic mechanism for the malformation in our case, one cannot ignore the topographical symmetry of the lesions, which are largely confined to the insular cortex. This could imply a circulatory disturbance: an argument canvassed for porencephalic defects which are often symmetrical, centred upon the insular region, and fringed by polymicrogyric areas. Alternatively, since cortical neuroblastic migration begins in the insula, the spatial pattern of the lesions may reflect the particular developmental stage which must be attained for induction of the polymicrogyric malformation.

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