

# Brain injuries in early foetal life: consequences for brain development

J Mancini\* MD;  
 V Lethel MD;  
 C Hugonenq MD;  
 B Chabrol MD, Department of Paediatric Neurology,  
 Paediatric University Hospital, La Timone, Marseille, France.

\*Correspondence to first author at address above.

Learning disability and cerebral palsy are often related to factors present before birth. We report three patients (two with schizencephaly, one with unilateral cerebellar agenesis) in whom the timing of an insult to the foetus was known. In the first case, the mother had a trauma at 16 weeks of pregnancy and schizencephaly was discovered in the male infant associated with a left hemiplegia. In the second child, amniocentesis performed at 16 weeks into pregnancy may have been responsible for the same cortical anomaly. In the third case, sequential foetal echographies clearly demonstrated that an apparent unilateral cerebellar agenesis was related to an haemorrhagic event secondary to cerebellar trauma that occurred at 19 weeks of pregnancy. It is suggested that these brain malformations are related to an ischemic mechanism or a traumatic event in foetal life.

Until recently, foetal brain damage was often attributed to intrapartum events but accumulated evidence suggests that learning disability\* and cerebral palsy are often related to factors present before birth. In some cases, because of medicolegal implications, dating brain injury should be of interest. We recorded three patients in whom the timing of a damaging stimulus to the foetus was known. Collecting information about such cases will serve to understand better underlying pathological mechanisms.

## Case reports

### PATIENT 1

At 16 weeks of pregnancy the mother of this boy was knocked down by a car. She was operated on for multiple consequent fractures. Then she was treated with heparin until delivery because of lower limb thrombophlebitis. Two foetal ultrasounds were normal. Foetal movements were present. There was no polyhydramnios. The boy was born without any problem at 36 weeks. The perinatal period was uneventful. Left congenital hemiplegia was diagnosed when the boy was 18 months old. Brain CT and MRI clearly showed a right-closed schizencephaly from the gyrus supramarginalis to the Rolandic area (Fig. 1). An arachnoid cyst was noted in the fronto-insular area. Outcome was good. Psychomotor acquisitions progressed at normal time. The boy was 12 years old at the time of follow-up. A slight left hemiplegia persisted with hemiatrophy especially on the leg. There was no epilepsy. Intellectual function was normal with good academic achievement.

### PATIENT 2

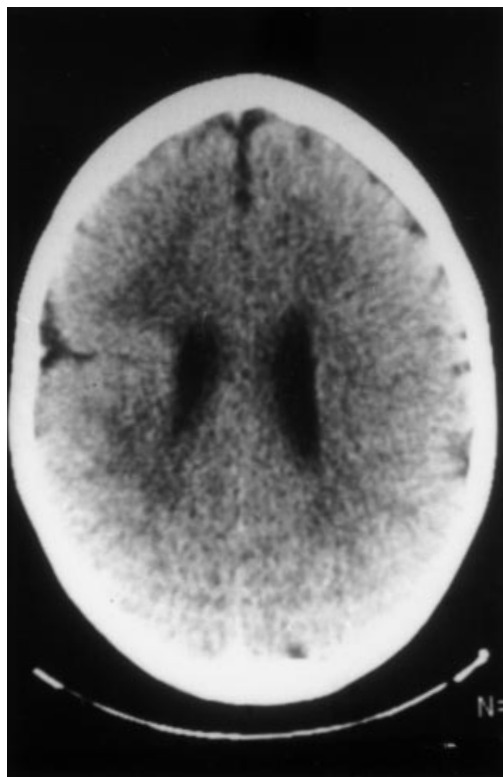
The mother's pregnancy at age 39 years was normal except that she underwent amniocentesis due to her age at 16 weeks. The puncture was difficult and, according to the mother, 'the needle struck against something'. Karyotype of the child was normal as were later sonograms. Delivery occurred at 40 weeks' without any special event. There was no specific mark on the scalp skin at birth. At 8 months of age this girl was hospitalized because of West syndrome. On

\*UK usage. US usage: mental retardation.

examination, a left-sided hemiparesis was noted. CT was performed at 10 months of age and showed large ventricular cavities with irregular walls. One month later, brain MRI showed closed schizencephaly at the level of the right insula (Fig. 2). At the time of follow-up this patient was 13 years old. She had a moderate right-sided hemiplegia. Seizures occurred less than once every 3 months. She has moderate learning disability (IQ=75).

#### PATIENT 3

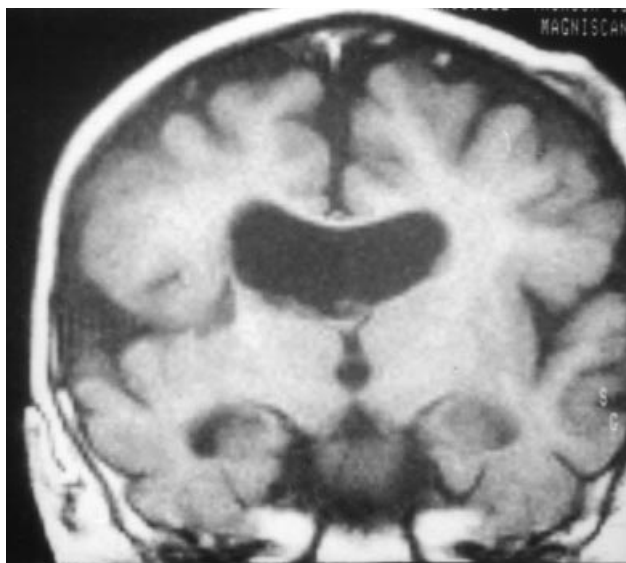
In this patient, timing of brain injury during pregnancy is accurately documented. At 17 weeks the mother underwent a direct abdominal trauma: she was violently kicked by her son who was lying near her. A foetal ultrasound was performed 3 days after this episode and showed a hyper echogenic structure in the posterior fossa that seemed to be vermian (Fig. 3) and was first considered to be a tumour. However, its evolution indicated a haemorrhagic event with a two component (hypo–hyper) echogenic aspect 2 weeks later. Foetal ultrasound 2 months after the trauma showed disappearance of these images and suggested that a left hypoplastic cerebellum had developed. A left cystic structure in the cerebellum was diagnosed with ultrasound 3 and 4 months later. Delivery was normal and at term. Psychomotor development was normal. At 3 years of age, there was only a slight tremor; intellectual function and language were normal. Brain MRI was performed at 28 months of age and showed cerebellar left hemisphere necrosis with mild atrophy of the brain stem especially of the right cerebellar pedunculus (Fig. 4).



**Figure 1:** Patient 1. CT of right closed schizencephaly from gyrus supramarginalis to Rolandic area.

#### Discussion

With MRI, brain cortical malformations are more easily diagnosed and some pathogenic aspects have begun to be elucidated. Cortical malformations should not be thought to result invariably from migration disorders. A genetic process is responsible for some cortical malformations such as lissencephalies type II, some lissencephalies type I, and band heterotopias (Des Portes et al. 1998) or even posterior agyria–pachygyria (Ferrie et al. 1995), and schizencephaly (Brunelli et al. 1996). However, in most cases cortical malformations are due to prenatal insults occurring during neuronal migration, between 12 and 20 weeks. Some recent animal models have served to explain pathological processes during pregnancy,



**Figure 2:** Patient 2. MRI of schizencephaly at level of right insula.



**Figure 3:** Patient 3. Prenatal ultrasound imaging of hyperechogenic structure in posterior fossa: post-traumatic haemorrhage.

using of ibotenate, a glutamatergic agonist. Using this substance during pregnancy in mice and hamsters has shown different types of brain lesions according to the timing of drug administration (Marret et al. 1995).

A causal relation between brain injury and cerebral abnormalities is obvious in patients 1 and 3 and possibly in patient 2. Whether the puncture during amniocentesis was responsible for the schizencephaly in patient 2 is difficult to determine. Usually, when amniocentesis is performed, the foetus is able to move far from the needle. Nevertheless some cases of brain injury due to amniocentesis (porencephaly), have been reported (Eller and Kuller 1995). In patient 1, the date of the mother's trauma fits well with the type of cortical malformation diagnosed some years later in her child. The term schizencephaly was first used by Yakovlev and Wadsworth to define a developmental defect as 'symmetric clefts in cerebral mantle during neuronal migration' (1946a, p 116). There are two theories concerning the pathogenesis of schizencephaly. The first, proposed by Yakovlev and Wadsworth, suggests a localized failure of induction of neural migration from the neural cells lining the primitive ventricle. Such a pathogenesis could be likely for patients reported as heterozygous for germline mutations in the homeobox gene *EMX 2* (Brunelli et al. 1996). The second theory is that an early destructive lesion involving a segment of the hemisphere can lead to schizencephaly; this mechanism is clearly documented in patient 1, in whom direct consequences of maternal trauma on the foetal brain could be responsible for a localized ischemic event. Alternately, heparin therapy could also have been involved. Schizencephaly with *in utero* warfarin exposure has been reported by Pati and Helmbrecht (1994). Nevertheless these

authors suggested that schizencephaly results from vascular accident and haemorrhage and not as a direct effect of warfarin on CNS morphogenesis. Schizencephaly is a regional disturbance of cerebral cortex formation. This process can occur when the cerebral mantle is thin enough to be destroyed. Clefts bordered by micropolygyria would result from a malacic process initiated between the 12th and 20th foetal weeks (Landrieu and Lacroix 1994). Ultrasound could not have diagnosed such an anomaly during pregnancy in our cases because they were type 1 schizencephalies (with closed lips and without any cystic component; Komarnisky et al. 1990).

In patient 3, a brain MRI performed at 2 years of age displayed a cerebellar left-hemisphere necrosis that mimicked unilateral cerebellar agenesis. A clearly documented follow-up showed that this unilateral agenesis was not a true malformation. The consequences of abdominal trauma were visualized on successive ultrasound examinations. Cerebellar trauma induced localized haemorrhagic infarction at 17 weeks of pregnancy; a subsequent necrosis led to a cystic lesion 6 weeks later. The same type of cerebellar lesion was reported in preterm children by Mercuri and colleagues (1997); these authors suggested a perinatal haemorrhagic/ischemic anoxic injury. In our case we believe it was a haemorrhagic/ischemic injury secondary to a trauma.

In this study, the brain malformations identified in these children are believed to have happened in foetal life, in association with an ischemic (or an haemorrhagic/ischemic) event either secondary to a maternal or foetal trauma. These brain injuries were related to events in the early midtrimester while most of the existing literature concerns later events (Murdoch Eaton et al. 1991, Cohen and Roesman 1994, Baethman et al. 1996). Owing to their early occurrence, we suggest that the injuries in these patients caused anomalies that mimicked congenital brain malformations.

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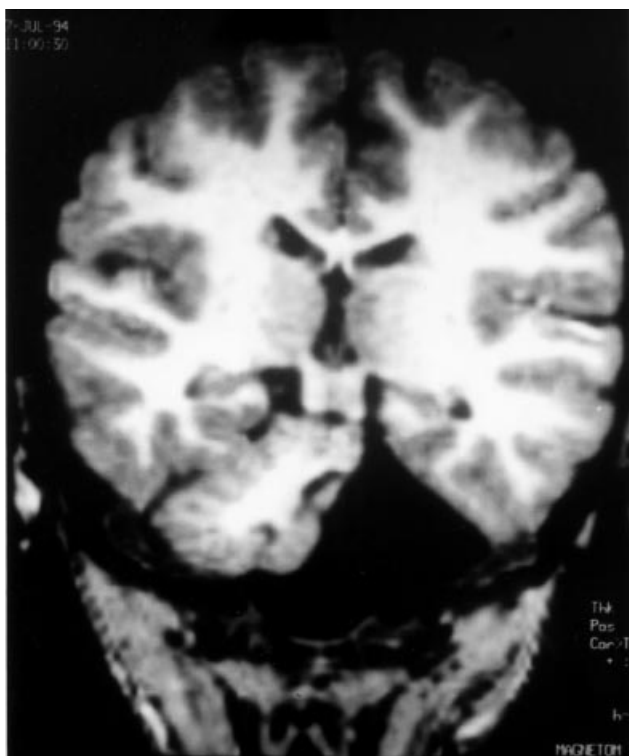


Figure 4: Patient 3. MRI of unilateral cerebellar post necrotic agenesis.

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# Notices

## **25th Annual Conference of the Michigan Association for Infant Mental Health. Hand in Hand: Multi-disciplinary Approaches to Supporting Relationships and Early Development**

*Michigan, USA, May 20–22, 2001*

This conference will focus on the relationships between parents and infants, families and providers, and the community systems needed to support the healthy growth and development of young children. Topics include cross-systems models for enhancing caregiving and child development; innovative programs and policies addressing infant, toddler, and family needs; fathers and their role as nurturers; family and professional partnerships; interdisciplinary communication in coordinating services; and creative solutions to institutional barriers. Tel: +1 734 764 4276, Fax: +1 734 764 1557. E-mail: [pully@umich.edu](mailto:pully@umich.edu)

## **5th International Congress on Cerebral Palsy**

*Bled, Slovenia, June 7–10, 2001*

The International Child Neurology Association (ICNA) second announcement and call for abstracts (submission date January 15, 2001). For further information see Web site: [www2.mf.uni-lj.si/~cp2001/index.html](http://www2.mf.uni-lj.si/~cp2001/index.html)

## **6th International Conference of Baltic Child Neurology Association**

*Kaunas, Lithuania, June 13–16, 2001*

For further information, please contact, Dr Nerija Vaiciene/ Dr Milda Endziniene, Department of Neurology, Kaunas University of Medicine, Eiveniu 2, LT–3007 Kaunas, Lithuania. Tel/Fax: (370-7) 330 423. E-mail [nerija.vaiciene@takas.lt](mailto:nerija.vaiciene@takas.lt). Web site: [www.info.kma.lt/BCNA](http://www.info.kma.lt/BCNA).

## **Society for Research into Hydrocephalus and Spina Bifida**

*Uppsala, Sweden, June 27–30, 2001*

Special session 'Monitoring of intracranial pressure at all ages'. Abstract forms (deadline February 16, 2001) and further details available from Ms CA Sobkowiak FCSP. Tel: +44 1325 465 033. Fax: +44 1325 465 033.

E-mail: [maureensrshb@btinternet.com](mailto:maureensrshb@btinternet.com)

## **4th Congress of the European Paediatric Neurology Society**

*Baden-Baden, Germany, September 13–16, 2001*

Dr F Hanefeld, President of the European Paediatric Neurology Society cordially invites you to participate in the forthcoming congress in Germany. For further information, please contact, AKM Congress Service GmbH, Obere Schanzstrasse 18, D-79576 Weil am Rhein, Germany. Tel: (+49) 7621 98 330. Fax: (+49) 7621 78 714. E-mail: [akmweil@akmcongress.com](mailto:akmweil@akmcongress.com). Web site: [www.akm.ch/epns2001](http://www.akm.ch/epns2001).