

NEUROPATHOLOGY 2000

Symposium On Developmental Neuropathology

A Satellite Meeting of the XIVth International Congress of Neuropathology
Oxford UK, September 1st 2000

ABSTRACTS



Developmental Neuropathology Symposium

Friday, 1 September 2000 – Chair: S Shorvon

Dysplastic and developmental causes of epilepsy: pathology, clinical features and treatment
sponsored by Janssen-Cilag Ltd

Lecture Theatre, St Anne's College

- 9.00 – 9.15 S Shorvon (Institute of Neurology, University College London)
Introduction: epilepsy and brain dysplasia
- 9.15 – 10.00 R Kuzniecky
Clinical features of epilepsy due to dysplasia. No abstract provided.
- 10.00 – 10.45 S Sisodiya
Imaging the dysplastic brain
- 10.45 – 11.15 Coffee
- 11.15 – 12.00 D Armstrong
Pathology of epileptogenic brain malformations
- 12.00 – 12.45 B Dobyns
Genetics of epileptogenic brain malformations No abstract provided.
- 12.45 – 2.00 Lunch – St Anne's College
- 2.00 – 2.45 G Mathern (Division of Neurosurgery, Los Angeles, USA)
Hippocampal pathology in children with epilepsy
- 2.45 – 3.30 H Cross (Dept of Neurology, Hospital for Sick Children, London)
Medical treatment for epilepsy due to dysplasia
- 3.30 – 4.15 C Polkey (Dept of Neurosurgery, King's College Hospital, London)
Surgical treatment for epilepsy due to dysplasia
- 4.15 – 4.45 Tea
- 4.45 – 6.00 Submitted papers

What is the relevance of Granule cell Dispersion to epilepsy?

Dr Brian Harding

Post-operative prognosis after long term follow up in childhood temporal lobe epilepsy:
neuropathologic correlates

Dr Yves Robitaille

7.30 for 8.00 Dinner, Somerville College

Saturday, 2 September 2000

Lecture Theatre, St Anne's College

Diagnostic dilemmas in developmental neuropathology

- 9.00 – 9.45 H Goebel (Mainz, Germany)
Extracerebral biopsy in neurometabolic diseases
- 9.45 – 10.30 Ian Rushton (Clanfield, Oxfordshire)
Acquired infant brain damage: the supporting evidence No abstract provided.
- 10.30 – 11.00 Coffee
- 11.00 - 12.30 Submitted papers

Patterns of Brain Damage in Infants with Congenital Heart Disease

Herwig Finkeldey

Developmental Malformations Of The Eye By Cyclophosphamide

Gisela Stoltenburg-Didinger

Neuropathology of repeated and prolonged cases of shaken-baby whiplash trauma cases

Akira Hori

Some developmental disorders of the pyramidal tract.

Hans J. ten Donkelaar

Psammoma Bodies in Human Fetal and Perinatal Adenohypophysis

Christopher U Schindler

1.00 Lunch – St Anne's College

Cortical Dysplasia and Epilepsy

Simon Shorvon

Institute of Neurology, University College, London, UK

Defects in the process of neuronal migration result in a number of disturbances in cortical development which can result in epilepsy. The classification of cortical dysplasia is currently unsatisfactory, and the most commonly used schemes rely largely on the appearances of the dysplastic tissue on histology or neuro-imaging. Recent advances in the genetic basis of neuronal migration have shed light on the underlying mechanisms, and will in time lead to a more rational classification and a better understanding of the process. Genetic studies with spontaneous and engineered mice mutants have defined at least four stages of cortical migration, and these probably have human correlates. Abnormalities at the onset of migration results in periventricular heterotopia, and have been shown to be due to mutations in the filamin 1 gene, which may act through modulation of the actin cytoskeleton. Lissencephaly and the double cortex syndrome are defects of the on-going process of migration. Mutations of two genes have been found to result in these malformations (LIS1 and Doublecortin) and may be due to abnormalities in the regulation of the microtubule cytoskeleton. Penetration of the migrating neurones through the subplate is the third stage of migration, and abnormalities in four mice genes have been shown to affect this process. The final stage of the penetration of migrating neurones through the cortical plate, and at least one gene has been found to influence this. Many of the genes controlling migration have biochemical links to the cytoskeleton, and abnormalities in the regulation of the cytoskeleton are probably key aspects in the production of the human dysplasias.

Imaging the Dysplastic Brain

Sanjay Sisodiya

Institute of Neurology, University College London, UK

In this review, the current state of imaging the dysplastic brain and achievements to date will first be considered. There remain a number of unanswered important questions in the biology of malformations, and in the second part of the talk, the potential for addressing these issues of state-of-the-art and evolving imaging methodologies will be considered.

Modern neuroimaging methods have already contributed significantly to our understanding of brain malformations. Thus PET and, especially, MRI have demonstrated the importance of malformations as causes of epilepsy, particularly refractory epilepsy, in both adults and children. Focal cortical dysplasia is, for example, likely to be the second most common nontumoural cause of refractory epilepsy and this abnormality is often well demonstrated on neuroimaging. In population studies, MRI has shown that malformations probably underlie 3% of cases of new onset epilepsy.

MRI has also been fundamental to the recent advances in the genetics of malformations. MRI has led to identification of phenotypes for linkage studies and the subsequent discovery of genes causing familial bilateral periventricular heterotopia, X-linked subcortical laminar heterotopia and lissencephaly, schizencephaly, lissencephaly with cerebellar hypoplasia and some cases of septo-optic dysplasia. Other genetically-mediated malformations may also soon be uncovered, such as familial polymicrogyria.

Key questions that remain include: what is basis of epilepsy in those cases when neuroimaging fails to reveal an underlying cause?; what might be the cause of malformations themselves?; what are the mechanisms of epileptogenesis?; and, lastly, what implications might there be for treatment?

Examples of how state-of-the-art and future neuroimaging of the apparently normal and dysplastic brain might help resolve some of these questions will be given. Consideration will be given in particular to:

- (1) the importance of quantitative analysis of neuroimaging data in revealing underlying malformations causing epilepsy, and histological correlation of such analyses.
- (2) the suggestion of new familial malformations and the future role of neuroimaging in genetic studies
- (3) the exploration of the mechanisms of epileptogenesis afforded by neuroimaging, including the definition of the epileptogenic zone and neuroreceptor studies
- (4) the impact of results from modern neuroimaging on formulating treatment strategies, including surgical treatment.

Imaging the Dysplastic Brain cont.

It is likely that imaging of the dysplastic brain will remain central to future research strategies aimed at improving our understanding of the biology of the dysplastic brain. Neuroimaging may be central not only to revealing the underlying causes of epilepsy, but also in the definition and understanding of concepts central to epilepsy associated with the malformed brain.

Pathology of Epileptic Brain Malformation

Dawna Duncan Armstrong

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The association between gross brain malformations and epilepsy has been recognised for over 50 years. However, the idea that microscopic malformations are also associated with epilepsy is a newer concept, and opens up the possibility that brain maldevelopment may be an important factor in many of the so-called idiopathic epilepsies. In this review the pathology of the gross malformations; lissencephaly, cortical dysplasia, cortical tubers, heterotopias and vascular malformations will be reviewed. All of these entities are becoming well known through imaging and genetic studies. However, the microscopic malformations, classified as microdysgenesis, are not yet readily identified by brain imaging techniques, and their recognition still requires the eye of the pathologist. The neuropathology of these “malformations” will be presented. Also morphologic aspects of the well studied ammon’s horn sclerosis that could be considered as microscopic malformations will be presented to illustrate how alterations in cytoarchitecture could produce an environment required for seizure genesis.

Hippocampal Pathology in Children with Epilepsy

Gary Mathern

Division of Neurosurgery; UCLA Medical Center, Los Angeles, USA

An important question for clinicians is whether early childhood seizures and/or the medications used to treat them adversely affect the structure and post-natal maturation of the developing brain. This is especially relevant for the hippocampus where childhood febrile convulsions have been speculated for many years to generate hippocampal sclerosis (HS) and mesial temporal lobe epilepsy (MTLE). Our laboratory has addressed these questions by examining hippocampi resected from pediatric epilepsy surgery patients with symptomatic temporal and extra-temporal substrates for cell loss, aberrant axon sprouting, and signs that post-natal granule cell migration is altered. To date, we have studied hippocampi from 67 surgical and 42 autopsy cases of similar ages (2 months to 17 years).

Results indicate that the degree of hippocampal pathology depends on the clinical epilepsy syndrome, and not the age at seizure onset or duration of epilepsy. Young patients with neocortical epilepsy from cortical dysplasia (CD; n=33), destructive pathologies (i.e. strokes and infections, n=14) or Rasmussen's encephalitis (n=8) show fascia dentata granule cell neuron loss, and signs of decreased post-natal granule cell migration and differentiation. In addition, mild aberrant mossy fiber sprouting into the fascia dentata inner molecular layer can be found as early as 8 weeks of age in children with CD and strokes. Longer seizure histories are not associated with increased hippocampal cell loss or aberrant axon sprouting in these children. By comparison, children with complex partial limbic epilepsy associated with hippocampal atrophy (n=6) and/or temporal lobe lesions (tumours and CD; n=6) show a pattern of neuron loss and mossy fiber sprouting consistent with adult HS. Very long seizure histories (i.e. greater than 15 years) are associated with increased CA1 and prosubiculum cell loss in MTLE patients.

These results support the hypothesis that HS is not the product of childhood seizures alone, but its pathogenesis must be associated with additional clinical mechanisms. Furthermore, the substrate that leads to HS probably evolves over time to become an epileptogenic focus in the temporal lobe. Mechanisms from animal experiments that might generate HS include local excitotoxic cell injury associated with epileptogenic temporal lesions, or other events, such as hypoxia/ischemia during seizures. Supported by NIH grants RO1 NS38992; and R55 NS36536.

Medical treatment of epilepsy due to cortical dysplasia

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The mainstay treatment of all epilepsy remains medication aimed at suppressing seizure occurrence. There are many anticonvulsant medications now available, with new medications on the market every year, with supposed known but varied mechanisms of action. A logical step would appear to target anticonvulsant medication according to known pathology and underlying epileptogenic mechanism. Unfortunately, although we have clues as to the likely pathophysiology in developmental abnormalities, data remains anecdotal and anticonvulsant use non-specific.

Abnormalities of development of the cerebral cortex appear to be associated with a high degree of epileptogenicity, and alongside this resistance to anticonvulsant medication. This is assumed from the high representation of such pathology within surgical series, although such series are likely to be subject to bias. The true incidence of medical resistance amongst developmental abnormalities, and indeed association with seizures remains unknown. In addition to date we have no clinical markers available to us as predictors of intractability.

Morphological, immunocytochemical and electrophysiological studies have provided some insight as to the probable mechanisms of epileptogenicity in the dysplasias but are only tantalising in their findings towards suggesting which medication may be advantageous in treatment. The wide range of differing pathologies would suggest different mechanisms of epileptogenicity and therefore response to different medications. Overall studies suggest that seizures arise as a result of an imbalance of excitation over inhibition, affecting a clinical relevant mass of neurons. This may involve neurotransmitter imbalance, maturity and/or morphology of neurons within the abnormalities. Current antiepileptic medication may be limited in their repertoire of action.

Although these studies are useful, in clinical practice at present it remains difficult to predict which individuals are likely to respond to antiepileptic medication or be drug resistant, and take on an approach to medical managements other than 'trial and error'. The lack of current understanding of epileptogenesis in the developmental malformations, and the imprecise nature many of the underlying mechanisms of action in the majority of the AEDs available to us imply that management has to be such, with medication directed at seizure type/syndrome rather than underlying pathology.

The Surgical Treatment of Cortical Dysplasia

Charles Polkey

King's College Hospital, London, UK

The surgical treatment of cortical dysplasia will be described in relation to 40 patients treated between 1976 and 1999 with a unique pathological diagnosis of cortical dysplasia and 21 patients with a unique diagnosis of DNET. The diagnostic criteria will be reviewed and the place of non-resective surgery, such as MST will be discussed. The place of dual pathology, found in 2 patients with CD, 3 with DNET and 6 others will be reviewed.

Among the patients with CD, eight underwent temporal lobectomy, 15 had frontal resections, seven major resections or hemispherectomy and 10 some other procedure. Among these 40 patients 30% became completely seizure free (1a) and in all these patients the removal was complete. 42.5% became seizure free according to Engel's group 1 criteria of whom 82% had a complete removal and in 27% there was no significant improvement in seizure control and only 9% of these patients had a complete removal. Neurological deficits in the form of a contralateral hemiplegia or hemiparesis only occurred in patients undergoing central or major resections. Unfortunately 6/8 patients undergoing central resections suffered such a deficit although in many patients there was considerable recovery.

Among patients with DNET, 18 underwent temporal lobectomy, there were two frontal resections and one lesionectomy. Among these 21 patients 42% became completely seizure free (1a) and in six of these nine patients (67%) the removal was considered complete. 62% became seizure free according to Engel's group 1 criteria and the removal was considered complete in 61.5% of these patients. No improvement in seizure control was seen in 19% of the group and in none of these was the removal considered complete. There were no serious neurological sequelae in these 21 patients.

The inevitable conclusion will be that the best surgical treatment of either pathology is complete removal of the lesion which is dependent upon its nature, visibility and location.

Extracerebral Biopsy in Neurometabolic Diseases in Children

Hans H. Goebel

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One neuropathological diagnostic way of looking at neurometabolic and neurodegenerative diseases in children is recognising whether their morphologic manifestation is confined to the central nervous system or whether they may also feature pathology outside of the brain. Brain biopsy as a diagnostic procedure is now largely obsolete because innumerable neurometabolic and neurodegenerative diseases in children have non-specific morphologic cerebral expression or when displaying disease-specific neuropathology it may be more easily and equally reliably recognised by extracerebral biopsy. Such neurodegenerative and neurometabolic diseases in childhood are those affecting intracellular organelles, foremost lysosomes and, to a lesser degree, mitochondria and peroxisomes or structures common to both the central and the peripheral nervous system, i.e. neuronal perikarya, axons, and glial/Schwann cells. The former are considered neurometabolic ones, i.e. lysosomal, mitochondrial, and peroxisomal disorders, the latter one, i.e. infantile neuroaxonal dystrophy, a non-metabolic neurodegenerative disorder, whereas Lafora disease is a polyglucosan disorder which assumes an intermediate nosologic position. The neurometabolic disorders may be further ascertained by biochemical and even molecular investigations whereas infantile neuroaxonal dystrophy is biochemically and molecularly unexplained. Hence, morphological studies, largely performed with the electron microscope, have different connotations. The ultrastructural investigation of biopsied extracerebral tissue in neurometabolic disorders is not obligatory, and had its prime in medical history some 20 to 30 years ago whereas infantile neuroaxonal dystrophy still may only be diagnosed with certainty before death by (extracerebral) biopsy. Among the three groups of neurometabolic disorders, the lysosomal conditions exhibit the most variable ultrastructural spectrum of lysosomes, the mitochondrial entities are rather limited in ultrastructural pathology of their organelle, the mitochondrion, whilst peroxisomal disorders show typical ultrastructural features which are actually not peroxisomes and peroxisomes are either absent, small, or normal, thus, only exhibiting quantitative differences. In certain lysosomal disorders, disease-specific ultrastructure may vary among different cell types and tissues whereas the infantile neuroaxonal dystrophic ultrastructural pathology appears rather uniform.

In the present molecular age, ultrastructural diagnostic pathology of neurometabolic disorders is largely a matter of the past. The neuronal ceroid-lipofuscinoses have recently undergone a dramatic nosological re-classification owing to a wealth of genetic information and thus, a shift from morphologic to molecular diagnosis is characteristic of the present. Only the still unexplained infantile neuroaxonal dystrophy remains to be recognised by morphology and that will remain in the future until genetic data in this autosomal-recessive disorder will be available. Based on this historiographic evolution of extracerebral neuropathology in neurometabolic

Extracerebral Biopsy in Neurometabolic Diseases in Children cont.

and neurodegenerative disorders of children it is foreseeable that ultrastructural neuropathological diagnostics will be reduced in the future, perhaps largely performed on clinical atypical and variant forms rather than classic neurometabolic and neurodegenerative diseases in children. This will render the neuropathologist's role more difficult, requiring greater experience rather than facilitate it.

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What is the relevance of Granule cell Dispersion to epilepsy?

Brian Harding

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Despite a century of epilepsy research, granule cell dispersion (GCD) was described only a decade ago. Houser and Lurton reported significant splaying of the granule cell ribbon in about half of temporal lobes resected from adults with temporal lobe epilepsy (TLE). Given the remarkably late final migration of granule cells, Houser pondered the relative importance of intrinsic maldevelopment or early seizural activity as possible disturbances of granule cell migration. Apart from adult surgical studies, the literature lacked any description of GCD, and many pathogenetically pertinent questions remained unanswered. How early does GCD appear in man, can it be bilateral, is it absolutely associated with epilepsy, and particularly TLE?

Morphologic studies from our pediatric epilepsy surgical programme have begun to address these questions. GCD is common in children with medically intractable epilepsy (46 of 105 hippocampal resections), is particularly but not exclusively associated with TLE and MTS (half of this group), and can also be found in children with extra-temporal epilepsy of various causes, or in the absence of other observable hippocampal damage. Post-mortem observations on 4 children indicate occurrence of bilateral GCD as early as 3 months, in 2 children unassociated with MTS or seizures. The significance of GCD in epilepsy must be reassessed: both intrinsic and acquired factors may play a role in its pathogenesis.

Post-operative prognosis after long term follow up in childhood temporal lobe epilepsy: neuropathologic correlates

Yves Robitaille

Department of Pathology, Ste-Justine Hospital, Montreal, Canada

We reviewed the clinical records of 22 pediatric patients who had temporal lobectomy for drug-resistant seizures between 1979-1999. All had partial-complex seizures, 48% with secondary generalization. Prior to surgery, seizures occurred daily in 69% with auras in 29%. One child had atypical febrile seizures. The mean age of onset for seizures was: 3.8±3.3y (range: 1m-10y). All but 2 subjects had "en bloc" resections, and there were 2 lesionectomies. The post-operative follow up range was 4m-19y (X=6.5±4.2y). A blind review of neuropathologic data was performed (YR). Cortical dysplasia was observed in 14 cases, with limbic extension in 2, and Mesial Temporal Sclerosis (MTS) in 3. Only 2 patients had isolated MTS. There were 2 benign lateral temporal tumours (Ganglioglioma=1, glio-neuronal=1), one of which was complicated by MTS and recurred. Post-operative results were: seizure free: 48% (10/21), 90% seizure frequency decrease: 29% (6/21), >50% seizure frequency decrease: 14% (3/21). 2 failed to improve at all, 1 was lost to follow up. We conclude that surgery affords substantial improvement of seizure control even to children with extensive cortical dysplasia.

Patterns of Brain Damage in Infants with Congenital Heart Disease

Herwig Finkeldey

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We assessed the morphological findings in the brains of 52 children with congenital heart disease. The average age was 440 days with a range between 1 day and 17 years. The relation male : female was 2 : 1. Forty seven children were treated surgically or/and catheterized and 30 of them were operated under cardiopulmonary bypass conditions. The main diagnoses were hypoplastic left-heart-syndrome (HLH n=7), transposition of the great arteries (TGA n=11) and complex malformation (CM n=8). Malformations of the CNS were seen in 25% of the children except those in the TGA group. Diffuse neuronal heterotopia was the most common finding. Gliosis was present in almost every brain. Immature cortical structures were found in 11 brains. The brain weight was reduced in 33 cases (63%). Twenty children showed infarcts, 5 showed sclerosis of the Sommer's sector, 36% had pontosubicular necrosis (PSN) and 66% of those also apoptoses in the fascia dentata, although most of these children were born at term and eutroph. The most surprising finding was the frequency of the haemorrhages: In 9 out of 25 children with this diagnosis it was the cause of death. The brain weight in the haemorrhage group was severely reduced in contrast to the brain weight in children without haemorrhage.

Developmental Malformations of the Eye by Cyclophosphamide

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Teratogenic effects of cyclophosphamide (Cy) include eye malformations and palatal clefts in humans. In an experimental model these effects were observed in the offspring of white Russian rabbits who received Cy by subcutaneous injection (12-15 mg/kg) during pregnancy (day 11 and 12 of gestation). Fetuses were examined between days 20 and 29. Additional to conventional histological stainings, immunohistochemistry was applied using the monoclonal antibody against Ki67. Apoptosis was detected by labelling the 3'OH-ends of fragmented DNA. In the fetuses of Cy-treated dams, a posterior coloboma involving the retinal pigment epithelium and optic nerve with associated abnormalities of the hyaloid vasculature and retinal dysplasia was seen in 15 of 60 eyes (25%), these changes were bilateral in most cases. In four of these eight fetuses simultaneous abnormalities of the palate occurred. Cy has been demonstrated to result in a severe perturbation of the cell cycle and to disrupt fusion processes during embryogenesis by augmenting apoptosis and inducing compensatory proliferation. In the eye, Cy can result in posterior coloboma formation which is rare in humans and usually associated with chromosomal abnormalities.

Neuropathology of repeated and prolonged cases of shaken-baby whiplash trauma cases

Akira Hori

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Shaken-baby whiplash syndrome is usually a fatal trauma (death within several days after trauma) characterised by a neuropathological trias: parasagittal subdural haematoma with or without subarachnoidal haemorrhage, retinal haemorrhage, and traumatic cervical changes. Additionally, contusions on the basal surface of the brain (olfactory/paraolfactory area) may be observed.

We present a case of a survived shaken-baby trauma with prolonged course and a case of repeated traumata.

In the prolonged case, not only subdural hygroma but also severe hypoxic encephalopathy with brain atrophy and hydrocephalus were observed. The victim was physically and mentally severely handicapped and died due to aspiration pneumonia in a bed-ridden condition 3 months after the initial trauma.

In the repeated trauma case, the initial traumatic changes such as rib fractures or retinal haemorrhage could not be recognised at necropsy. It is possible that the victim did not only get shaken whiplash trauma but also additional complex traumata during the abuse. These complications may make the post mortem diagnosis difficult.

Some developmental disorders of the pyramidal tract

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The pyramidal tract, the main central motor pathway in man, can be absent due to a variety of developmental disorders. A familial, non X-linked case of severe microcephaly, and a case of porencephaly both with bilateral absence of the pyramids will be presented.. The first case concerns two siblings (a female and a male neonate) who died as neonates and had severe microcephaly, bilateral absence of the pyramids, and dysplastic inferior olives reaching the midline. The aqueduct was not stenotic. Microscopically, the corticospinal tracts were severely hypoplastic or absent. The cerebral hemispheres otherwise showed a more or less normal gyral pattern with an incompletely covered insula, and a torn but otherwise intact corpus callosum. This rapidly fatal, familial syndrome, probably transmitted as an autosomal recessive trait, has several features in common with the Neu-Laxova syndrome. The second case is a severe form of porencephaly in a male neonate who died three months after birth. Bilateral destructive lesions of so far unknown origin involved the somatomotor areas of the cerebral cortex. Severe hydrocephalus possibly due to or leading to aqueduct stenosis and bilateral absence of the pyramids with midline displacement of the inferior olives was found.

Psammoma Bodies in Human Fetal and Perinatal

Adenohypophysis

Christopher U Schindler

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- 3) Institute of Neuropathology, University of Giessen, Giessen, Germany

We report on the phenomenon of 'psammoma bodies' in the development of human pituitary gland. These mineralisations containing calcium and iron each begin to appear in the 16th week of gestation, reach the peak of density in perinatal age, and disappear nearly completely in the first year of life. They are localised in the lumina of age-typical folliculi or diffusely in the endocrine parenchyma.

In our study the appearance of the pituitary calcifications was examined systematically in a collective of normal and malformed fetuses of different developmental stages; the results suggest a physiological embryological phenomenon. As possible causes the high cellular turnover in the developing gland, a degenerative thickening of the basal lamina (like Crooke's hyaline change) or a relative surplus of prolactin are discussed.

In our mind this phenomenon should not be interpreted as a regressive change (e.g. following hypoxia or intrauterine infection). A significant in- or decrease in malformations (esp. malformations injuring the hypothalamo-hypophysial axis) was not found.