ORIGINAL ARTICLE

The Lissencephalic Syndromes

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Summary

Lissencephaly is a rare disorder resulting from aberrant neuronal migration within the brain. It is found in a heterogenous group of disorders which results in profound mental retardation and severe neurological complications. We report 2 infants with lissencephaly – one with Miller-Dieker syndrome, and another with cerebro-cerebellar lissencephaly. A better clinical delineation of the phenotypic features as well as recent advances made in neuroimaging techniques and molecular genetics have resulted in significant improvements in the classification, genetic counselling and prenatal diagnosis for this devastating disorder of lissencephalic syndromes.

Key Words: Neuronal migration disorder, Mental retardation, Molecular genetics, Genetic counselling

Introduction

Although lissencephaly implies "smooth brain"[1], in reality lissencephalic brains may be agyric or associated with pachygyria. It is an uncommon congenital malformation of the brain arising from abnormal neuronal migration from the 10th to 15th week of gestation. The normal cerebral cortex consists of six horizontal layers with nervous cells stratified along these layers. In lissencephaly there is arrest in development with only four layers of cortex being formed. Histologically the cells remained in a mainly columnar arrangement with loss of stratification. This generalised deranged migration of neuroblasts results in the abnormal formation of gyri and sulci[2].

Neuropathologically two major types, type I and type II are recognised[3]. Type 1 lissencephaly is found in Miller-Dieker syndrome (MDS) and isolated lissencephaly sequence (ILS). MDS consists of severe type 1 lissencephaly, characteristic craniofacial and other associated abnormalities. Type II lissencephaly usually lacks characteristic facies but may be associated with retinal dysplasia, posterior fossa abnormalities, congenital muscular dystrophy and hydrocephalus. The Walker-Warburg syndrome, cerebro-oculo-muscular syndrome and cerebro-cerebellar lissencephaly are such examples[4].

In recent years, MDS and ILS have been better defined with definite clinical, cytogenetic and molecular features. Deletions in the lissencephaly critical region on chromosome 17p13.3 have so far only been found in MDS and ILS[3]. These findings, along with newer developments in cerebral imaging techniques have significant implication in genetic counselling and prenatal diagnosis. We report two infants who presented with severe neurological abnormalities and subsequently diagnosed to be lissencephalic syndromes, namely MDS and cerebro-cerebellar lissencephaly.

Case 1

A 3-month-old male Chinese infant was admitted to the University Hospital Kuala Lumpur for chest infection and failure to thrive. He was delivered via normal vaginal delivery in another hospital with a birthweight of 2.6 kg. The pregnancy was uneventful and the parents were non-consanguinous. His three other siblings were normal. There was no significant past, family or medical history.

Postnatally he had mild neonatal jaundice and stridor. The parents also noted that the child progressively deteriorated with poor feeding, weak cry and failure to thrive. He had an average of five tonic convulsions

daily associated with staring eyes and central cyanosis with each episode lasting 1-2 minutes. Two days prior to admission, he had fever, cough and breathlessness.

On examination during this admission, his weight was 3.3 kg (< 3rd percentile), length 54 cm (< 3rd percentile), occipitofrontal circumference 36 cm (< 3rd percentile). He was noted to have dysmorphic features consisting of prominent forehead with bitemporal furrowing, anteverted nostrils, prominent thin upper lip and micrognathia (Fig. 1a). He was tachypnoeic, pale and had inspiratory stridor. Examination of the chest revealed subcostal recession and generalised coarse crepitations. A soft ejection systolic murmur of grade 2/6 was heard on auscultation over the left sternal edge. He had marked opisthotonus with a hyperextended neck and increased extensor tone (Fig. 1b). There was scissoring of the lower limbs with up-going plantar reflexes. No ankle clonus was elicted. The fundi were normal.

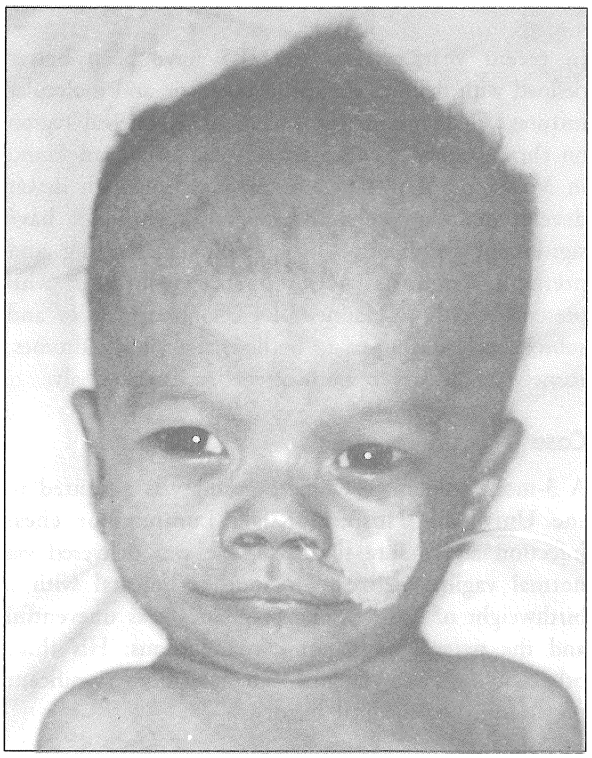

Fig. 1a: Patient photograph showing prominent forehead, bitemporal furrowing, anteverted nostrils, prominent thin upper lip and micrognathia

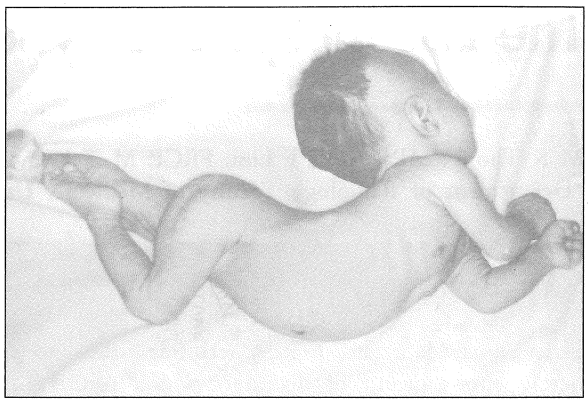

Fig. 1b: Marked opisthotonus of patient with a hyperextended neck and increased extensor tone

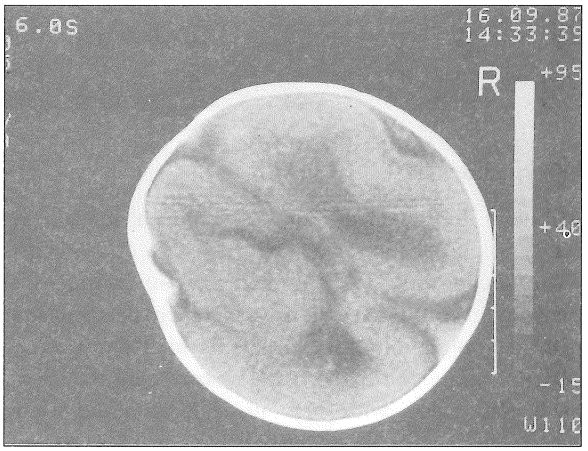

Fig. 1c: Computerised tomography of patient – generalised agyria was clearly seen

The patient's respiratory condition rapidly deteriorated and needed ventilatory support. The full blood count and serum electrolytes were normal. Chest radiograph showed bilateral patchy infiltrates consistent with bronchopneumonia. Cultures of the blood and cerebrospinal fluid yielded no growth. Titres of serum antibodies to toxoplasma, rubella, cytomegalovirus (CMV) and herpes were not elevated. Chromosomal studies later revealed a normal 46XY karyotype. Molecular studies by using chromosome-specific probes were not available in our institution. Metabolic screening of blood and urine for the presence of amino-acids and organic acids were negative. A small ventricular septal defect was demonstrated on

echocardiography and changes consistent with partial epilepsy were seen on electroencephalogram (EEG). Computerised tomography of the brain revealed generalised agyria (Fig. 1c). Together with the dysmorphic features, a diagnosis of Miller-Dieker Syndrome was made.

He was ventilated for one week, given penicillin and gentamicin, intravenous fluids and phenobarbitone. The patient recovered and at 11 months, he still had marked opisthotonus and global neurodevelopmental and physical growth delay.

Case 2

A newborn Chinese boy was referred for evaluation of neonatal seizures. He was born at term, to a 30-year-old G1P0 mother after an uneventful pregnancy. Both parents were healthy and unrelated. The family history was non-contributory. His condition at birth was good: Apgar scores being 9/10 and 10/10 at 1 and 5 minutes respectively. He weighed 3.2 kg at birth (50th percentile) and the occipitofrontal circumference measured 33 cm (10th - 25th percentile).

On the second day of life, he was noted to have several episodes of twitching of the face and jerky movements of both upper limbs. He was thus referred for further management. On admission to our institution, no dysmorphic features were noted and the rest of the physical examination including the neurological examination and fundoscopy did not reveal any abnormality. Investigations done showed Hb: 161 g/l, platelet count $230x10^9$/l, total white blood count $12.1x10^9$/l with polymorphs 64% and lymphocytes 34%. Serum sodium 138 mmol/l, potassium 4.5 mmol/l, chloride 99 mmol/l, serum calcium 2.1 mmol/l and magnesium 0.65 mmol/l. Random blood glucose was 3.8 mmol/l. Results of cerebrospinal fluid analysis was normal. CSF and blood cultures were sterile. Titres of serum antibodies to toxoplasma, CMV, herpes and rubella were not elevated. EEG showed frequent sharp waves and spikes of high voltages over the frontal and temporal regions bilaterally. Subsequently C.T. scan of the brain (Fig. 2) revealed dilatation of both lateral ventricles and suprasellar cisterns with hypoplasia of the cerebellum. The brain surface was relatively smooth suggestive of deficiency in sulci and gyri. A diagnosis of cerebro-cerebellar lissencephaly was made. Chromosome study was a 46XY karyotype.

Phenobarbitone (5mg/kg/day) as a single nocte dose was commenced and fits were under control. He was discharged on day ten of life. At six weeks follow-up, he weighed 4.3 kg (10th - 25th percentile) and the occipito-frontal circumference measured 34.3cm (<3rd percentile). His neurodevelopment was markedly delayed and his seizures recurred but these were controlled by increasing the dose of the anticonvulsant.

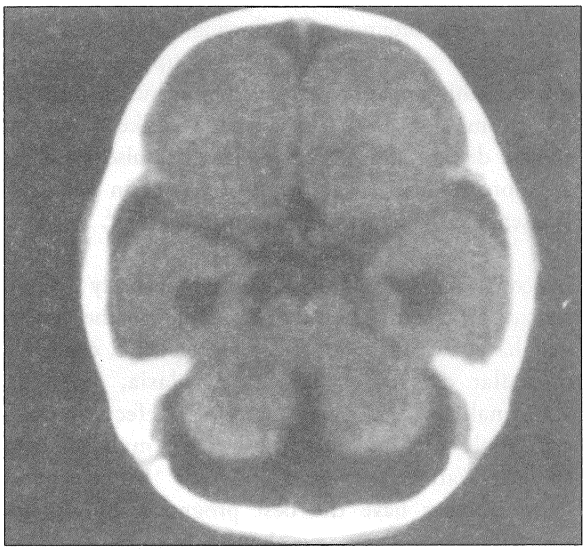

Fig. 2: C.T. scan of brain – showing dilatation of both lateral ventricles and suprasellar cisterns with hypoplasia of the cerebellum. Note the smooth brain surface suggesting deficiency of sulci and gyri

Discussion

Lissencephaly is a rare congenital defect of the brain[1]. Miller in 1963[5] and Dieker *et al* in 1969[6] described lissencephaly to be associated with a malformation sequence in two siblings and four other patients, respectively with postnatal growth deficiency, craniofacial defects and severe neurodevelopmental dysfunction. However, it is not a pathognomonic feature as the defect can occur by itself or as a clinical feature of a malformation syndrome[7]. With better

delineation of phenotypic features, availability of magnetic resonance imaging (MRI) or computerised tomographic (CT) scan and high resolution chromosome analysis, a better understanding of these heterogenous conditions and their prognosis have been achieved in recent years.

As profound mental retardation, microcephaly and other severe neurological abnormalities are always present in patients with lissencephaly, the diagnosis of MDS requires the presence of a severe type I lissencephaly with grossly normal cerebellum, and certain characteristic craniofacial features such as frontal bossing with bitemporal hollowing, short nose with anteverted nostrils, prominent upper lips and micrognathia[4]. In ILS these dysmorphic features are not prominent. Other abnormalities like congenital cardiac defects and growth deficiencies also occur. In addition, midline calcification of the brain with type I lissencephaly is pathognomonic of MDS[4].

In contrast, type II lissencephaly usually has no characteristic craniofacial features, although the patients may have macrocephaly from hydrocephalus, congenital muscular dystrophy, retinal dysplasia, cerebellar abnormalities and posterior fossa defects such as encephalocele and Dandy-Walker malformation (Walker-Warburg syndrome, WWS)[2,4]. The isolated lissencephalics have the best prognosis and longest survival[2]. Prenatal cytomegalovirus infection has been implicated in some cases of isolated lissencephaly[8].

Radiologically, the CT scan and MRI features can be divided into primary or secondary findings[9]. The primary finding is usually indicative of a neuronal migration defect which consists of a completely smooth brain that is agyric or areas of pachygyria. The sylvian grooves may be shallow and the distribution of white matter throughout the brain may be scanty. In MDS, the brain is agyric or almost agyric, whereas in ILS, the cerebral surface is more variable – ranging from agyria to complete pachygyria[3]. Secondary features include hydrocephalus, colpocephalus (dilatation of posterior horns of lateral ventricles), absent corpus callosum and Dandy-Walker malformation. These features are important clues to diagnose type II lissencephaly. The EEG findings are usually characterised by abnormally fast and very high-voltage activity in the alpha and beta frequency bands. Gastaut *et al* proposed that this "major fast dysrhythmia" is virtually specific for lissencephaly when seen before the age of one year and may permit antemortem electroclinical and pathological correlation[10].

The lissencephaly syndromes were once thought to be autosomal recessive disorders based on reports of familial occurrence in the past. Cytogenetic abnormalities were first described in patients with MDS in 1983[11] and these were later confirmed by somatic cell hybrid studies with probes from the 17p13.3 region which detected molecular deletions in 90% of the patients studied, including seven in whom high resolution chromosome analysis was normal. Twelve per cent of these deletions were the result of familial rearrangements[4]. The first case of ILS with a microdeletion was reported in 1991[12].

Further diagnostic advances were made by using fluorescent in-situ hybridisation (FISH) and polymerase chain reaction (PCR) assay to identify a dinucleotide repeat polymorphism[3]. With these new findings, MDS appeared to be de-novo events in some patients, or from abnormal segregation of familial balanced translocation in others. In addition, the parental origin of these abnormalities can be ascertained through various molecular techniques and the appropriate genetic counselling can be given to the affected families. It is recommended that high resolution chromosomal analysis followed by FISH be carried out on all patients with type I (MDS and ILS) or atypical lissencephaly[3] and if a deletion is not found in cases of MDS and ILS, other aetiologies and diagnoses should be carefully considered. Prenatal diagnosis by either chorionic villous sampling or amniocentesis is therefore feasible for these families in institutions with these diagnostic facilities.

The prognosis of children with lissencephaly is grim, with 50% mortality rate at the age of 6 months[3]. The survivors are severely mentally retarded and have severe neurological complications. Supportive management and genetic counselling are the mainstay of treatment.

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