Extreme Microcephaly, Diffuse Agyria, Agenesis of Corpus Callosum, Cerebellar Hypoplasia with Dandy-Walker Malformation: Is This A Severe Form (Barth Syndrome) or A New Variant of Microlissencephaly

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Author(s): Aneja H, Saikia B, Patel A, Sural A

Abstract

A five month girl with extreme microcephaly and complex brain malformation is reported. Magnetic resonance imaging (MRI) revealed bilateral thickened smooth cortex with diffuse agyria-pachygyria spectrum, agenesis of corpus callosum, bilateral hypoplastic cerebellar hemispheres and ventriculomegaly with Dandy-Walker malformation. By adding our case in the list of similar case reports by László Sztriha [1] and Mitsuhiro Kato [2], we suggest a possible classification of a new variant of microlissencephaly.

Introduction

Lissencephaly refers to rare malformations that share the absence of normal circumvolutions of the cerebral cortex. Has several subtypes as described by Dobyns and Leventer and the classification is based on associated malformations and etiologies. [3]

Out of the five different subtypes i.e. classic lissencephaly, lissencephaly X-linked with agenesis of corpus callosum (ARX gene), lissencephaly with cerebellar hypoplasia (LCH), microlissencephaly and cobblestone lissencephaly, microlissencephaly and LCH syndrome shares some overlapping features, major cause of heterogeneity being different gene mutations responsible for gross brain malformations in both cerebral and cerebellar cortices. [4]

We report a case of microcephaly with diffuse agyria and pachygyria, agenesis of corpus callosum, bilateral hypoplastic cerebellar hemispheres and ventriculomegaly with Dandy-Walker malformation. With almost similar case reports by László [1] and Mitsuhiro [2] but with interesting associated finding of Dandy-Walker malformation, this could well be a distinct variant of microlissencephaly (like Type A and Type B) with a possible classification among the lissencephaly syndromes.

Case Report(s)

Five month female child, born to nonconsanguinous parents presented with multiple episodes of seizures for past one month. Born at full term by cesarean section, indication being fetal distress; baby cried immediately after birth with good APGAR score. Antenatal ultrasound was suggestive of microcephaly. Perinatal period was uneventful. Weight (4.5 kgs) and length (56 cms) were percentile for age. Head circumference was 32cms (rdpercentile for age). There was no history of hypothyroidism, inborn error of metabolism (sensorial alteration, recurrent episodes of poor feeding, lethargy and tone abnormalities) or congenital malformations. There was no family history of seizures.

On examination, the child had bitemporal hollowing, anteverted nostrils with broad nasal bridge, receding forehead, thin vermilion border of upper lips, retrognathia and posteriorly angulated auricles. There were no skeletal deformities and neurocutaneous markers. There was generalized hypotonia with global development delay. Other systemic examination including ophthalmological examination was normal. Child was having refractory seizures in spite of being phenytoin 8mg/kg/day, valproate 40 mg/kg/day and clobazam 0.5mg/kg/day.

Magnetic resonance imaging (MRI) of brain revealed thickened smooth cortex with absent sulcations and shallow vertically oriented sylvian fissures giving 'figure of eight' configuration to the cerebrum suggestive of lissencephaly. There was associated agenesis of corpus callosum, ventriculomegaly and fourth ventricle communicating with posterior fossa cyst suggestive of Dandy-Walker malformation. There was hypoplasia of bilateral cerebellar hemispheres. [Illustrations 1-5] X-ray chest and spine, abdominopelvic ultrasound scan and Echocardiography was normal. Thyroid profile, creatine phosphokinase (CPK), liver and renal function tests were normal.
Discussion

Lissencephaly describes a smooth brain; it refers to rare malformations that share the absence of normal circumvolutions of the cerebral cortex. There are several types and classification (Dobyns and Leventer, 2003), based on associated malformations and etiologies. Five major groups of lissencephalies can be recognized. [3]

This rare brain formation disorder is caused by defective neuronal migration during the 12th to 24th weeks of gestation, resulting in a lack of development of brain folds (gyri) and grooves (sulci). It is a form of cephalic disorder. Children with lissencephaly are severely neurologically impaired and often die within several months of birth. [5]

Microlissencephaly differs from classical lissencephaly and other variants by the presence of severe microcephaly, resulting from an abnormal neuronal proliferation or survival combined to neuronal migration disorders. Two main types are recognized: Type A (previously called the Norman-Roberts syndrome with no infratentorial anomalies) and Type B (or Barth syndrome) which is associated with severe hypoplasia of cerebellum and corpus callosum. [3]

László Sztriha has described a case of extreme microcephaly with agyria-pachygyria, partial agenesis of the corpus callosum and pontocerebellar dysplasia [1]. Whereas Mitsuhiro Kato reports two families with diffuse pachygyria and cerebellar hypoplasia and proposed it to be a milder form of microlissencephaly. [2] Similar cases have been reported by Miyata [6] and Farah [7] respectively with the possibility of new lissencephaly syndrome. There have been only two case reports of lissencephaly (and not microlissencephaly) from India prior to this. [8] Our case has similar findings to that of László Sztriha and Mitsuhiro Kato with interesting finding of Dandy Walker malformation. By reporting this case, we are adding one more in the list of microlissencephalies syndrome. Therefore, we propose it to be a genetically distinct variant of microlissencephaly with a possible classification among the lissencephaly syndromes.

Acknowledgement(s)

Dr. Zubair Ahmed Lone and Dr. Pompa Dutta, Department of Pediatrics, St Stephens Hospital, Delhi-54

Authors contribution(s)

Dr Himanshu Aneja and Dr Aneet Patel are involved in the work-up of the case.
Dr Bedangshu Saikia has contributed in finding out the references and writing the discussion.
Dr Anuradha Sural, a consultant in Radiology, has contributed in the radiology part

References

5. Lissencephaly: wikipedia search

Description of Illustrations

Illustration 1 and 2 are Magnetic Resonance Images of Brain (Axial T1 and T2 respectively) showing thickened smooth cortex with absence of sulcations and 'figure of eight' configuration to the cerebrum suggestive of lissencephaly associated with agenesis of corpus callosum.

Illustration 3 and 4 Magnetic Resonance Images of
Brain (Sagital T1 and T2 respectively) showing associated agenesis of the cerebellar vermis and the fourth ventricle communicating with posterior fossa cyst suggestive of Dandy walker malformation. There was hypoplasia of bilateral cerebellar hemisphere.

**Illustration 5** Magnetic Resonance Diffusion Weighted Image of Brain showing thickened smooth cortex with absence of sulcations and 'figure of eight' configuration to the cerebrum suggestive of lissencephaly associated with agenesis of corpus callosum.
Illustrations

Illustration 1

MRI Brain (Axial T1)

Illustration 2

MRI Brain (Axial T2)
Illustration 3

MRI Brain (Sagital T1)

![MRI Brain (Sagital T1)](image1)

Illustration 4

MRI Brain (Sagital T2)

![MRI Brain (Sagital T2)](image2)
Illustration 5

MRI Brain (DWI)
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Reviews

Review 1

Review Title: extreme microcephaly, diffuse agyria, agenesis of corpus callosum, cerebellar hypoplasia with Dandy-walker malformation: Is this a severe form (? Barth syndrome) or a new variant of microlissencephaly

Posted by Dr. Rashna Dass on 20 Nov 2010 02:29:27 AM GMT

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<td>Can you suggest brief additions or amendments or an introductory statement that will increase the value of this paper for an international audience?</td>
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Rating: 5

Comment:

A. ABSTRACT:
1. In the abstract, the word "possible classification" should be replaced by "subtype"
2. Case report(s)- should be singular
3. Was screening for congenital infections done? This should be mentioned since CMV infection is associated with microcephaly with cerebral migration abnormalities
4. Vermian hypoplasia and degree of hypoplasia (above or below the level of 4th ventricle) needs to be mentioned
5. Cerebellar hypoplasia also needs to be shown in an illustration. Description of cerebellar folia and hemispheres- whether normal foliation or dysplastic needs to be clarified.

B. DISCUSSION:
1. The statement- "It is a form of cephalic disorder"- is redundant and should be deleted
2. Statement- "Children with lissencephaly die within several months of birth" (Reference no 5 from Wikipedia search)- is wrong data. Please review and revise from peer reviewed journal. Prognosis differs according to various factors- whether MDS or isolated lissencephaly. Significant proportion of patients with isolated lissencephaly live till 10 years of age.
3. Barth syndrome- Mendelian inheritance in Man Data (MIM ID # 302060) documents barth syndrome as a disorder with cardio-skeletal myopathy with neutropenia with abnormal mitochondria. this syndrome does not include lissencephaly or Dandy walker spectrum. reference quoted is not from peer-reviewed journal. May exclude

C. REFERENCES:
1. Needs to be arranged in standard format - authors surname first name initial. journal article title. Journal name. Year;Issue:page nos.

D. ILLUSTRATIONS:
1. Legend of illustration 3 & 4- It is not agenesis of vermis- it is hypoplasia of cerebellar vermis above the level of 4th ventricle.

2. Illustration 5- It is a repetition of ilustrations 1 & 2 which also show figure of 8 appearence. It is suggested that this image be removed and in place add an axial image at the cerebellar level

NOTE: Review process was assisted by valuable and critical comments on the images and text matter by Dr Anindita Sinha, Assistant Professor in charge of MRI, Dept. of Radiodiagnosis, NEIGRIHMS, Shillong-18 email: dranindita@gmail.com

Competing interests: none

Invited by the author to make a review on this article? : Yes

Experience and credentials in the specific area of science:
general pediatrics, Pediatric intensive care, Infectious disease, rheumatology

Dr Anindita Sinha's expertise- Magnetic resonance imaging, MR spectroscopy, Interventional radiology

Publications in the same or a related area of science: No

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