NEW SYNDROME

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Profound Microcephaly, Primordial Dwarfism with Developmental Brain malformations: A New Syndrome

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We describe two sibs with a lethal form of profound congenital microcephaly, intrauterine and postnatal growth retardation, subtle skeletal changes, and poorly developed brain. The sibs had striking absent cranial vault with sloping of the forehead, large beaked nose, relatively large ears, and mandibular micro-retrognathia. Brain magnetic resonance imaging (MRI) revealed extremely simplified gyral pattern, large interhemispheric cyst and agenesis of corpus callosum, abnormally shaped hippocampus, and proportionately affected cerebellum and brainstem. In addition, fundus examination showed foveal hypoplasia with optic nerve atrophy. No abnormalities of the internal organs were found. This profound form of microcephaly was identified at 17 weeks gestation by ultrasound and fetal brain MRI helped in characterizing the developmental brain malformations in the second sib. Molecular analysis excluded mutations in potentially related genes such as *RNU4ATAC*, *SLC25A19*, and *ASPM*. These clinical and imaging findings are unlike that of any recognized severe forms of microcephaly which is believed to be a new microcephalic primordial dwarfism (MPD) with developmental brain malformations with most probably autosomal recessive inheritance based on consanguinity and similarly affected male and female sibs.

Key words: lethal microcephaly; interhemispheric cyst; fetal magnetic resonance imaging; autosomal recessive inheritance; microcephalic osteodysplastic primordial dwarfism; Amish microcephaly; microhydranencephaly; microlissencephaly

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INTRODUCTION

Microcephaly is a morphological sign that used to describe patients more than three standard deviation (SD) head circumference below the mean for a given age, gender, and race [Abdel-Salam and Czeizel, 2011]. Whereas microcephaly means a small head, micrencephaly is the accurate term for a small brain. Since the growth of the skull in general is initiated by the growth of the brain, both terms could be used. Microcephaly is a neurodevelopmental disorder that usually results from failure of neurogenesis. It could stem from various genetic and environmental etiologies. Thus, it could be congenital or postnatal, primary or secondary, isolated or as a part of multiple congenital abnormalities [Abdel-Salam and Czeizel, 2011]. The autosomal recessive simple form is characterized by reduction in the brain size but preserved brain architecture [Abdel-Salam and Czeizel, 2011]. On the other hand, lissencephaly results from defect of neuronal migration but of normal brain volume. These two findings together have been referred to as "microlissencephaly". The genetic basis and mechanistic causes of microlissencephaly are still unknown [Sztriha et al., 1998; Alkuraya et al., 2011].

Genes that induce neural progenitor proliferation versus differentiation are of particular interest, because the shifts in the balance between proliferation and differentiation may explain the evolution and differences in brain size among mammals [Kriegstein et al., 2006; Fish et al., 2008]. Abnormal spindle-like microcephaly associated (*ASPM*) gene was hypothesized to be one of the genetic

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components underlying the human brain expansion [Zhang, 2003]. Expansion has been through increased surface area rather than increased cortical thickness [Rakic, 2009]. This has been accommodated topologically by folding of the cerebral cortex to form convolutions, so that there is a transition from the smooth cortical surface seen in rodents to one of multiple folds in humans [Ponting and Jackson, 2005]. In general, sulci form as internal physical forces within the cerebral parenchyma, secondary to proliferation of cells and cellular growth including neuritis and glial processes that form the neuropil. The sequence of this normal growth is genetically programmed and precise, resulting in predictable timing of the formation of sulci and gyri in the cerebral cortex. In the case of severe micrencephaly due to either deficient cellular proliferation or accelerated apoptosis, sulci do not develop because there is no need to increase the surface area of the cortex without a concomitant increase in mass or volume of the tissue [Sarnat, 1992].

Brain imaging is considered indispensable in the evaluation of patients with microcephaly and fetal magnetic resonance imaging (FMRI) has been increasingly used recently for evaluation of brain malformations in-utero [Saleem and Zaki, 2010].

We report here on a novel syndrome in two sibs born to a young Egyptian consanguineous couple presented with profound microcephaly, intrauterine and postnatal severe growth retardation, and minimal skeletal dysplasias. Brain imaging showed extremely simplified gyral pattern, large interhemispheric cyst, abnormal cerebral ventricular system with very small part of the occipital region of lateral ventricles and 4th ventricle, abnormally shaped hippocampus and proportionately small cerebellum and brainstem.

CLINICAL REPORT

Patient 1

This patient is the first child of healthy double consanguineous (first maternal and second paternal cousins) Egyptian parents. The mother and father were 19 and 22 years old, respectively, at the time of birth. There is no relevant family history. The mother had no history of trauma or irradiation exposure. Moreover, TORCH examination, complete blood picture, blood sugar, and blood pressure records of the mother were normal. The pregnancy was complicated by mild oligohydramnios and ultrasound scan in the 32nd week of gestation showed severe intrauterine growth retardation with very small biparietal diameter (BPD). A male child was born at term by spontaneous vaginal delivery. His birth weight was 950 g (−4.8 SD), length, head circumference, and Apgar scores were not recorded although he was noticed to have severe microcephaly. There were no post-natal problems except of the poor gain of weight but he was discharged 40 days after birth.

He was referred to our clinic for genetic counseling because of severe microcephaly and growth retardation. On physical examination at the age of 40 days, weight was 1250 g (−3.3 SD), length was 39 cm (−5.6 SD), and OFD was 23 cm (−8.8 SD). He had very small head with absent cranial vault and remarkable slope of the forehead. Normal scalp hair, prominent and overhanging nasal tip, and relatively large simple ears were noted (Fig. 1). The phalanges and nails appeared normal. The external genitalia were normal male. His neurological evaluation revealed increased tone in the arms and legs with brisk deep tendon reflexes and flexor planter responses. Moro reflex, rooting reflex, and grasping reflex were present. Brain MRI (Fig. 2) at the age of 40 days, showed poorly developed gyri with thin cortex, large interhemispheric cyst, agenesis of corpus callosum, no ventricles are seen but very small part of the occipital region of lateral ventricles and 4th ventricle and abnormally shaped hippocampus. The size of cerebellum and brainstem looks proportionate to the very small cerebral hemisphere. No clinical evidence of primary pulmonary, cardiac, or renal diseases. At the age of 50 days he developed partial seizures. An EEG done at this time showed disturbed background activity with marked suppression of amplitude along all brain areas especially on the left side. He had a history of repeated vomiting. There

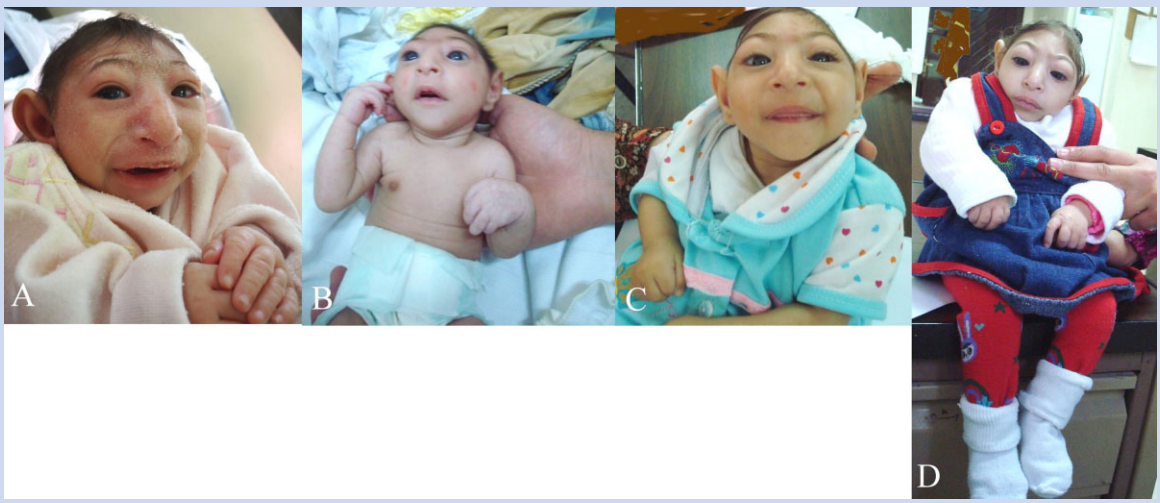

FIG. 1. Patient 1 (A) at 40 days of age. Patient 2 (B) at the age of 2 months (C) at 7 months (D) at 11 months. Note the striking similarity of extreme microcephaly, absent cranial vault, sloping forehead, beaked nose, relatively large ears, and micro-retrognathia.

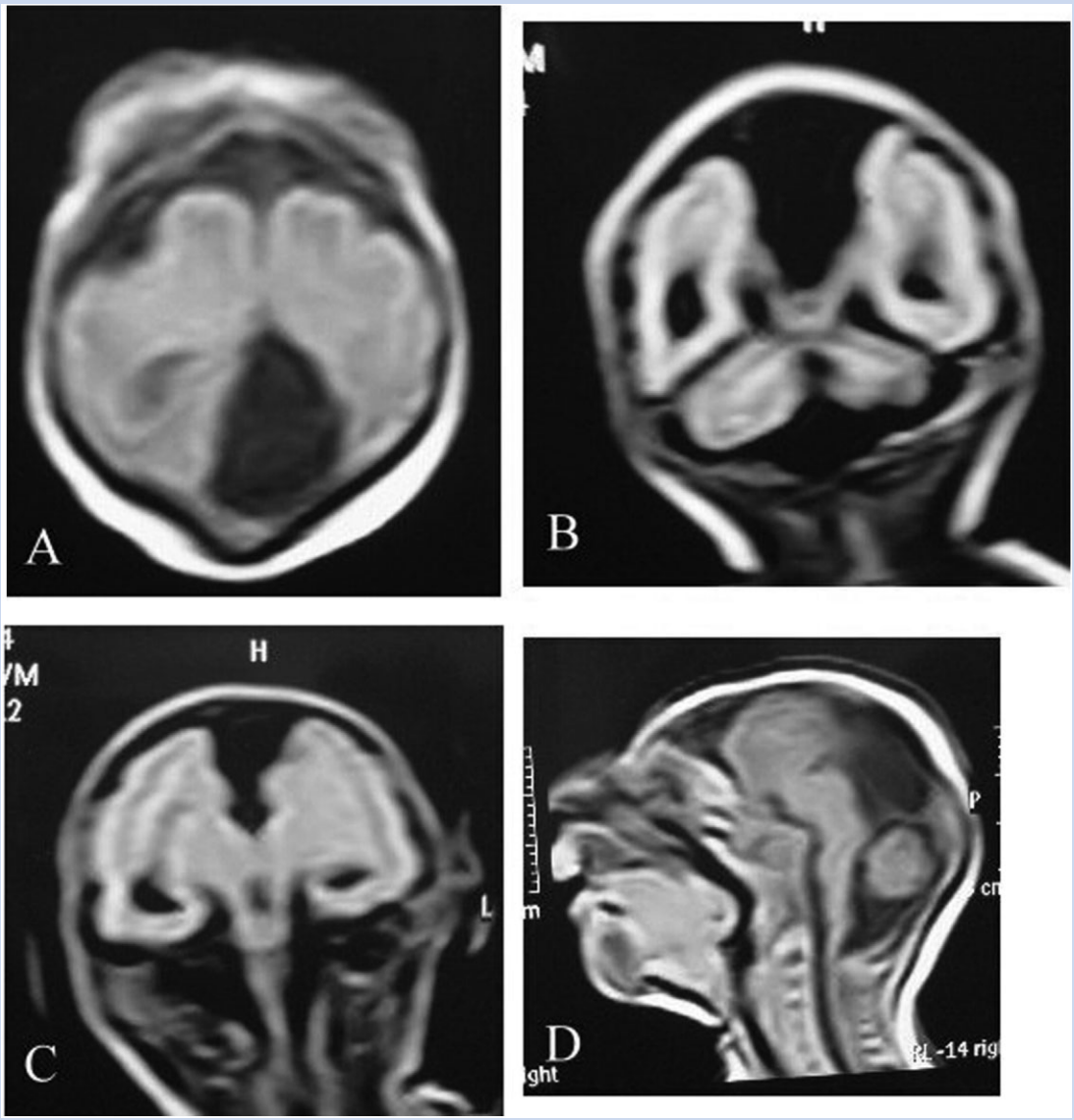

FIG. 2. Brain MRI of Patient 1 showing (A) axial view of abnormal gyral pattern, (B) coronal view with interhemispheric cyst and hypoplastic cerebellum, (C) abnormal hippocampus, (D) sagittal view showing agenesis of corpus callosum, hypoplastic vermis and pons but of proportionate size to the small cerebral hemispheres.

was no history of irritability. He had hypertonia and hyperreflexia but there were no contracture or other localizing neurological signs. Ultrasound examination of the abdomen and an echocardiogram were normal. Examination of his fundi showed foveal hypoplasia with bilateral optic atrophy. A TORCH screen was negative. Repeated urinary amino and organic acid screens in particular 2-ketoglutarate were unremarkable. Serum ammonia, lactate, hematological indices, and liver function tests were all reported as normal.

Radiographic examination showed very small anterior fontanelle, opened but overriding sutures, and very large eye sockets. The long bones of the upper limbs were relatively short with metaphyseal broadening. Chromosomal examination from peripheral blood lymphocytes revealed normal male karyotype 46, XY. FISH (fluorescent in-situ hybridization) studies were performed, which ruled out 13q deletion. Just before death, he was afebrile when admitted to hospital for artificial ventilation because of episodes of apneic spells. He died at age 70 days. Permission for autopsy was refused.

Patient 2

She was the younger sister of Patient 1. Head size was closely monitored during pregnancy and fetal ultrasonography at 17 week of gestation showed a BPD of 28 mm, an abdominal circumference of 108 mm, and a calculated OFC of 106 mm and at 19 week of gestation showed a BPD of 32 mm, an abdominal circumference of 129 mm, and a calculated OFC of 120 mm (−10th centile). At

31 weeks, BPD was at 50 mm (< 3rd centile). Fetal brain MRI was arranged at 20 weeks of gestation (Fig. 3). It showed underdeveloped brain especially that involves the frontal lobes as well as the posterior cerebral hemispheres. No evidence of gyral development and non-identifiable sulci were observed. Agenesis of corpus callosum with communication of the anterior interhemispheric fissure with the third ventricle, underdeveloped pons with flattened pontine flexure, and small sized cerebellum with a small transverse cerebellar diameter measure 14.6 mm that corresponds to 14–15 weeks were documented. The size of cerebellum and brainstem looks proportionate to the very small cerebral hemisphere. No other gross fetal anomalies were noted. Further, craniofacial distortions is recognized with frontal sloping, a nearly absent cranial vault, and small mandible. The results of the imaging studies and their interpretation were discussed with the parents and termination of the pregnancy was presented as a possible option and was declined by the parents.

A baby girl was born at 40 weeks of gestation by standard vaginal vertex delivery. Her weight, length, and OFC were 1,300 kg (−3.7 SD), 36 cm (−6.9 SD), and 21 cm (−8.1 SD), respectively. She had very severe congenital microcephaly with similar facial features like her deceased brother including absent cranial vault, sloping of forehead, prominent and overhanging nasal tip, relatively large simple ears, and micro-retrognathia (Fig. 1). Sacral sinus and clenched hands were also noted. Neonatal reflexes (Moro, rooting, and grasping) were present. Brain MRI at the age of 2 weeks confirmed the findings of the fetal MRI showing extremely simplified gyral pattern with thin cerebral cortex, poorly developed olfactory groves and non-identifiable olfactory bulbs, large interhemispheric cyst and proportionately affected cerebellum and brain stem. Irritability with inconsolable crying was noted in the first weeks of life, requiring occasional sedation. Seizures started at the age of 2 months in the form of partial seizures and her EEG showed slow waves with superimposed fast activity. Seizures showed good response on phenobarbitone and valproate.

She had a weak suck with poor weight gain and by 5 months, her weight, length, and OFC were 2,200 kg (−6.5 SD), 43 cm (−9.6 SD), and 23 cm (−12 SD), respectively. All sutures fused and the anterior fontanel was closed. She suffered from repeated vomiting. At that age bilateral inguinal hernia was observed. Further, she started to be visually aware of the environment, she could track objects but she does not recognize her mother. She was cooing and smiling spontaneously and she could bring her hands to her mouth. Neurological examination showed hypertonia of the extremities and deep tendon reflexes were increased bilaterally with flexor planter responses.

Skeletal radiological examination (Fig. 4) at the age of 7 month showed posterior narrowing of the ribs with splayed anterior ends, the long upper and lower bones were undermodeled with metaphyseal broadening. Further, the pelvis showed horizontal acetabular roofs and unossified pubic bones.

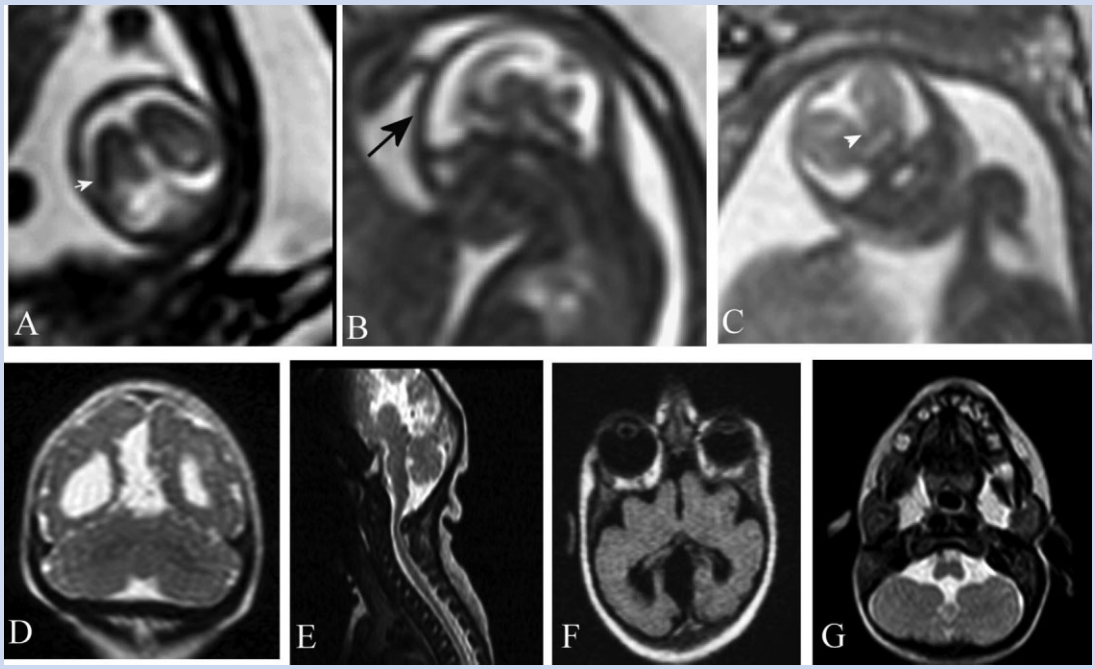

FIG. 3. Fetal MRI brain of Patient 2 at 20 gestational weeks. A: Coronal view showing poor developed cortex (white arrow) and the interhemispheric cyst. B: Sagittal T2-weighted bSSFP shows interhemispheric cyst (black arrow), hypogenesis of corpus callosum, enlarged cisterna magna, underdeveloped pons with flattened pontine and small sized cerebellum but of proportionate size to the small cerebral hemispheres. C: Axial view showing proportionately small cerebellum (white arrow head). Postnatal brain MRI of Patient 2. D: Coronal view showing extremely simplified gyral pattern, thin cerebral cortex, and interhemispheric cyst. E: Sagittal view showing agenesis of corpus callosum but proportionately affected cerebellum vermis and pons. F: Axial view showing abnormal gyral pattern and too shallow sulci. G: Proportionate small cerebellum and brain stem.

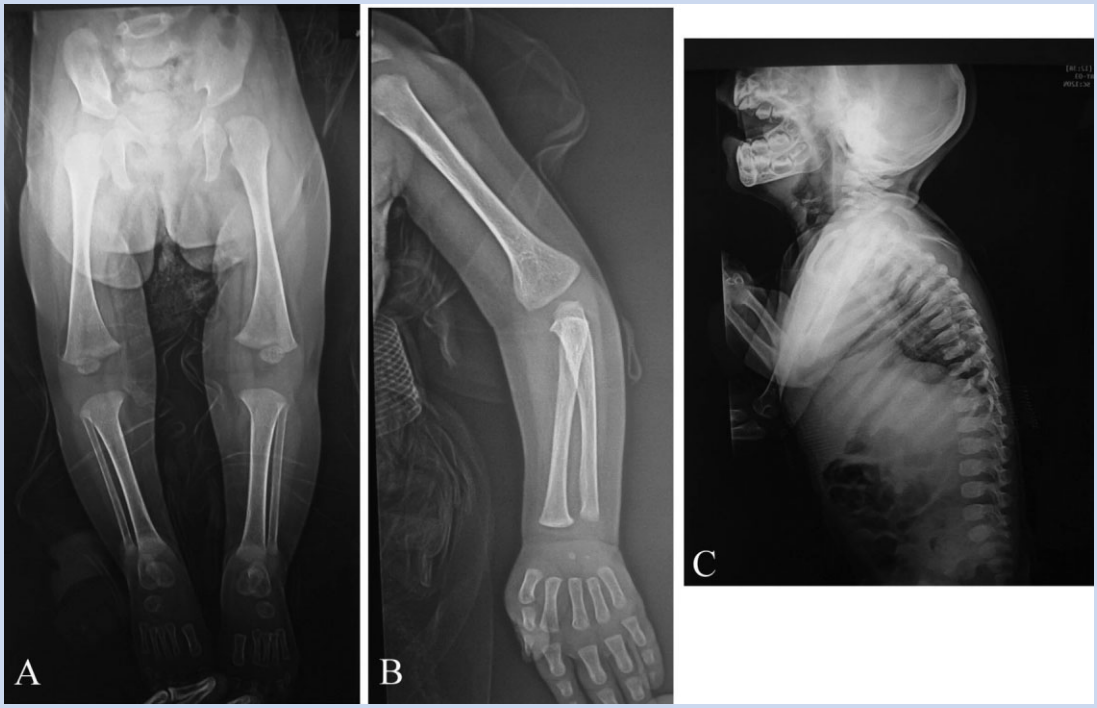

FIG. 4. X-Ray of Patient 2 at the age 7 months showing (A) abnormal configuration of the iliac wings, horizontal and smooth acetabular roofs. There is incomplete ossification of the pubic bones and slight metaphyseal flaring, (B) thin cortex with metaphyseal flaring of humerus, (C) platyspondyly of the thoracic spines and splaying of the ribs.

Follow up at the age of 10 months showed weight, length, and OFC: 2,800 kg (−5.9 SD), 46 cm (−9.5 SD), and 24.5 cm (−13.9 SD), respectively. The girl became spastic with clenched hands. No intention tremors were observed. She could hold her head but she could not lift up her head when placed in prone position. She could kick with her legs in supine position to roll. Dental examination showed that two of the lower incisors had erupted. The teeth were small but proportionate to the dental arch. At 14 months, her anthropometric measures did not show any gain in weight, length, or head circumference and she has made no further developmental progress. In addition, she had repeated attacks of hematemesis. Her hemoglobin dropped to 8.5 g/dl. Investigation of her hematemesis did not reveal a bleeding dyscrasia. She showed good response on omeprazole. She died at age 15 months after frequent attacks of hematemesis and seizures. Permission for autopsy was declined.

Chromosomal examination from peripheral blood lymphocytes revealed normal female karyotype 46, XX.

MUTATION ANALYSES

This research was reviewed and approved by the Research Ethics Committee of the National Research Centre according to "World Medical Association Declaration of Helsinki" and written informed consent was obtained.

Genomic DNA was extracted from peripheral blood leukocytes of the two patients and their parents using QIAamp® DNA Mini Kit (QIAGEN, Germany). Due to the overlap with microcephalic osteodysplastic primordial dwarfism I (MOPD I), the *RNU4ATAC* gene was amplified according to He et al. [2011]. Further, the entire coding region and exon-intron boundaries of the *SLC25A19* and *ASPM* genes were amplified using specific primers, thus excluding Amish microcephaly and simple isolated microcephaly, respectively. The sequence of primers and PCR cycling conditions are available upon request. No pathogenic mutation has been identified in any of the three genes.

DISCUSSION

We report on a novel syndrome which consists of intrauterine and postnatal growth retardation, profound congenital microcephaly (head circumference −8 SD below the mean at birth), developmental brain malformations (extremely simplified gyral pattern, large interhemispheric cyst, agenesis of corpus callosum, and abnormally shaped hippocampus) and subtle skeletal dysplasias in the form of dysplastic hip and metaphyseal broadening. This combination is very similar to MOPD I caused by mutations in the *RNU4ATAC* [Edery et al., 2011; He et al., 2011]. In fact, there is a wide range regarding the type and severity of brain, skeletal and genital anomalies, degree of motor and speech delay, and survival observed in MOPD I patients even among siblings [Abdel-Salam

et al., 2011, 2012; Nagy et al., 2011]. Although interhemispheric cyst, lissencephaly, and microlissencephaly were described in many of MOPD I patients [Vichi et al., 2000; Klinge et al., 2002; Edery et al., 2011; Juric-Sekhar et al., 2011], but the brain MRI of MOPD I patients are quite distinct in that there was a cortex with variable thickness from normal to thickened in others consistent with neuronal migration defect. Moreover, MOPD I patients usually have sparse or absent hair and very dried and aged skin and unlike our patients do not have such severe sloping of forehead, beaked nose, and large ears. Nevertheless, the *RNU4ATAC* gene in the patients described here was normal.

Seckel syndrome is another autosomal recessive condition of MPD with characteristic facial features in the form of sloping of the forehead, beaked nose, and micro-retrognathia similar to our patients. Although neuronal migration abnormalities are not common in Seckel syndrome and only four patients were reported with agenesis of corpus callosum, hypoplasia of the cerebellar vermis, and a dysgenetic cerebrum with pachygyria and a medially located dorsal cyst [Krishna et al., 1994; Shanske et al., 1997], the brain images of our patients are quite different showing extremely simplified gyral pattern. Moreover, many features described in Seckel syndrome were not present in our patients. These include bilateral clinodactyly of fifth finger and cryptorchidism in males. Finally, the presence of dysplastic bone changes and the disproportionate growth retardation made this diagnosis unfavourable. MOPD II syndrome and Caroline Crachami syndrome (MOPD III) seem unlikely to be relevant from a clinical and radiological viewpoint [Majewski, 1992].

Amish microcephaly is another autosomal recessive condition that we considered. We thought about this because of the profound microcephaly, the sloping of the forehead and the abnormal gyral pattern, agenesis of corpus callosum, and hypoplasia of cerebellum and brain stem [Kelley et al., 2002; Siu et al., 2010]. Further, Amish microcephaly patients showed foveal hypoplasia and mild skeletal changes such as subluxation of the femurs, coax valga, and osteopenia. However, Amish microcephaly patients usually had mild intrauterine and postnatal growth retardation. This condition was excluded because levels of keto-glutaric acids as well as sequencing of the *SLC25A19* showed normal results. We presume that the sloping of the forehead present is due to the underdeveloped forebrain.

Rajab et al. [2007] reported on four patients from the same family with a lethal form of microcephaly. All sibs died in the neonatal period following severe apnea attacks and central hypoventilation. The patients of Rajab et al. had an apparently different condition as the brain imaging showed well-developed brain but with mildly simplified gyral pattern and small corpus callosum, brainstem, and cerebellum. Further, our patients did not show hypoventilation or apnic spells and early demise that characterize the four sibs described by Rajab et al. [2007].

Another cause of profound microcephaly with variable encephaloclastic brain lesions and early lethality, which is attributable to intrauterine vascular interruption for example, following vascular accidents, cocaine addiction, or co-twin vascular disruption [Russell et al., 1984; Hahn et al., 2003]. This picture is sporadic and known as fetal brain disruption sequence. The severity of the brain injury is time related showing hydranencephaly when insult occurs between 20 and 27 weeks of gestation while similar injuries after 27 weeks tend to cause multicystic encephalomalacia with astroglial reaction. Unlike this condition, our patients did not have hydranencephay or multicystic encephalomalacia [Corona-Rivera et al., 2001; Hahn et al., 2003]. We are aware with the reported familial cases with microhydranencephaly, but these patients showed quite different brain imaging findings [Behunova et al., 2010].

It is noteworthy to highlight the three families with sib recurrence of a phenotype which resembles fetal brain disruption sequence suggesting autosomal recessive pattern of inheritance [Alexander et al., 1995; Schram et al., 2004]. These patients showed underdevelopment of the cerebral hemispheres with a smooth surface surrounded by a great amount of cerebrospinal fluid, ventriculomegaly, and hypoplastic corpus callosum. The cerebellum was hypoplastic in few patients but the brainstem was normal in all. Unlike our patients these patients did not show either severe congenital microcephaly or intrauterine growth retardation but progressive microcephaly ensued with time. Furthermore, the two sibs described here had absent cranial vault with sloping of the forehead. In contrast, all the sibs described with fetal brain disruption sequence showed normal cranial vault with characteristic scalp rugae [Alexander et al., 1995; Schram et al., 2004].

It is important to mention the condition of atelencephalic microcephaly (Table I). These patients had also profound microcephaly with small neurocranium at birth, scalp rugae, hypertonia, and practically no psychomotor development [Ippel et al., 1998]. Unlike our patients, patients with atelencephalic microcephaly have hardly any ventricular system (except for the 4th ventricle, without their replacement by CSF), only a very small amount of CSF and more or less normal cerebellum and brain stem. Furthermore, although atelencephaly is mostly sporadic, one report of familial occurrence in two siblings from a consanguineous relationship has been reported [Florell et al., 1996]. Finally, patients with atelencephaly do not present with severe intrauterine and postnatal growth retardation.

Sztriha et al. [1998] reported on three sibs with extreme microcephaly, very thin brain mantle with agyria-pachygyria, agenesis of the corpus callosum, and severe hypoplasia of the brainstem and cerebellum. Sztriha et al. [1998] categorized the brain imaging findings as microlissencephaly. However, Sztriha's patients have severe hypoplastic cerebellum and pons and did not have interhemispheric cyst. Thus, they had an apparently different condition as brain imaging was distinct from our patients. Further, the three male sibs had micropenis and arthrogryposis multiplex congenital and they lived for few hours.

We are aware of the two male patients with lethal microcephaly described by Fabian et al. [2001]. Although, these patients showed poor gyral pattern and cortical maturation, absence of corticofugal tracts and corpus callosum, agenesis of the optic pathway with preserved eyes, and facial dysmorphism, but they showed skeletal anomalies such as arachnodactyly, camptodactyly, genu recurvatum, and genital anomalies, in addition. The absence of these skeletal and genital anomalies and the recessive mode of inheritance suggest that our patients represent different condition from that described by Fabian et al. [2001]. Nevertheless, it is still possible that the patients described by Sztriha et al. [1998], Fabian et al. [2001]

TABLE I. Comparison of the Novel Syndrome With Those in the Differential Diagnosis

	Novel syndrome	MOPD I (OMIM # 210710) [Abdel-Salam et al., 2012; Nagy et al., 2011]	Seckel (OMIM # 210600) [Shanske et al., 1997; Al-Dosari et al., 2010]	Amish microcephaly (OMIM # 607196) [Kelley et al., 2002; Siu et al., 2010]	Fetal brain disruption sequence [Alexander et al., 1995; Schram et al., 2004]	Atelencphaly [Ippel et al., 1998]
Intrauterine growth retardation	Severe to profound	Severe to profound	Less severe (proportionate)	Mild	Normal to mild	Mild
Postnatal growth retardation	Severe to profound	Severe to profound	Less severe (proportionate)	Mild	Normal to mild	Mild
Mean OFC at birth in SD	−8 SD	−7 SD	−5 SD (proportionate)	−6 SD	−0.6 to −4 SD	<−7 SD
Clinical features	Sloping forehead, prominent and overhanging nasal tip, relatively large ears, and mandibular micro-retrognathia	Sloping forehead, prominent eyes, prominent nose with downturned tip, and small posteriorly rotated ears	Sloping forehead, prominent and overhanging nasal tip, relatively large ears, and mandibular micro-retrognathia	Sloping forehead, prominent and overhanging nasal tip, relatively large ears, and mandibular micro-retrognathia	Reduced neurocranium ridged skin of the head, prominent glabella prominent nose, retrognathia, and large ears	Sloping forehead, prominent eyes, severely malformed calvaria with overlying rugged skin.
Brain imaging findings	Poorly developed gyri, large interhemispheric cyst, agenesis of corpus callosum, abnormally shaped hippocampus, hypoplastic pons, and an underdeveloped cerebellum and vermis.	Agenesis of corpus callosum, lissencephaly, interhemispheric cyst, cerebellar hypoplasia and polymicrogyria.	Agenesis of corpus callosum, hypoplasia of the cerebellar vermis, and a dysgenetic cerebrum, pachygyria, midline cyst.	No gyral development, hypoplastic pons, and an underdeveloped cerebellum	Severely underdeveloped small and smooth brain surrounded by a large amount of cerebrospinal fluid.	Intact cranial bone, neither cerebral hemispheres, nor ventricles, and normal medulla, cerebellum and pons
Skeletal findings	Dysplastic hip and metaphyseal broadening	Short and bowed long bones, broad metaphyses, poorly developed acetabula, dislocated hips, platyspolndyly, splaying of ribs	No skeletal malformations except for dislocation of the radial head and dysplastic hip.	Diffuse osteopenia, bilateral coxa valga, and mild lateral subluxation of the proximal femurs, closed spinal dysraphism.	Not reported	Kyphosis, bilateral talipes equinovarus
Laboratory findings	—	—	—	High keto-glutaric acids	—	—
Gene	Unknown	*RNU4ATAC*	*CEP152,CENPJ, ATR*	*SLC25A19*	Unknown	Unknown

and our patients could represent the same spectrum with variable severity but the incomplete knowledge and the rarity of cases may account in part for confusion.

Such profound microcephaly is also described in holoprosencephaly and Neu-Laxova. We have excluded these disorders based on the clinical and brain imaging findings and normal cytogenetic studies.

We think this developmental brain malformation due to arrested proliferation in the 11–12 weeks of gestation following telencephalic cleavage as the presence of brainstem and cerebellar structures as well as normal prosencephalic cleavage, with predominant involvement of the forebrain along with absent gyri, goes in favor of an insult at around.

To the best of our knowledge, the cerebral malformations reported here are different from those described in previous classifications of simple isolated microcephaly with a simplified gyral pattern or microlissencephaly. In addition, the phenotype differs from those with MOPD, Amish microcephaly, and fetal brain disruption sequence (Table I), thus representing, in our view, a novel syndrome which was not previously recognized.

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