

Association of Infantile Spasms and Hypsarrhythmia with Primary Microcephaly- Three Case Reports

Dear Editor,

Autosomal Recessive Primary Microcephaly is a rare developmental anomaly characterized by a small head size with variable degrees of mental retardation in genetically predisposed children. We report three children who presented with microcephaly, psychomotor retardation, infantile spasms and hypsarrhythmia. All these children had mutations of the WDR 62 gene which contributed to microcephaly, mental retardation, and infantile spasms. Children who present with cryptogenic West Syndrome should be evaluated with clinical exome sequencing to rule out genetic causes for this childhood epileptic encephalopathy after exclusion of routine metabolic and infectious causes.

[What is known] Autosomal Recessive Primary Microcephaly is an autosomal recessive disease manifesting with hypsarrhythmia and epilepsy leading to psychomotor retardation, developmental delay and a poor scholastic performance.

[What is new] In the context of a child presenting with a phenotype of microcephaly and epileptic encephalopathy, clinical exome sequencing may be considered to detect genetic mutations that contribute to a small head size after infective and metabolic causes have been ruled out. In children who present with hypsarrhythmia, prompt treatment of epilepsy reduces the seizure burden and improves the cognitive outcome in affected children.

Case 1 was a 3-month old female, born to non-consanguineous parents [Figure 1a Pedigree chart], full-term normal vaginal delivery with an Apgar of 8 at 1 minute and 8 at 5 minutes. Her birth weight was 2750 grams, head circumference 32 cm [below the 10 th centile] and length 48 cm. At 3 months of age, there was a delayed social smile, poor neck

control and repeated jerks on awakening. On examination, baby was alert with ill sustained gaze, poor neck control, hypotonia and hyporeflexia. Serum lactate, ammonia and Toxoplasma, Rubella, Cytomegalovirus and Herpes virus IgG and IgM were negative. Tandem Mass Spectroscopy was normal. **Interictal EEG** [Figure 1b] consisted of a chaotic background rhythm with asynchronous high voltage slow waves, independent spikes and polyspikes suggestive of a hypsarrhythmia. **MRI** of brain [Figure 1c] was normal. **Genetic studies:** [Figure 1d] Clinical exome sequencing of the baby revealed a **homozygous** mutation in exon 30 in WDR 62 gene [from C > A at c. 3878]. Baby received adrenocorticotrophic hormone, pyridoxine, and valproate. Follow up at 6 months of age revealed a global developmental delay and the encephalogram revealed a slow background activity with no epileptic discharges.

Case 2 was a female baby born to non-consanguineous parents by caesarian section at 37 weeks of gestation [Figure 2a pedigree chart]. Baby was appropriate for gestational age with a birth weight of 2500 gm, head circumference of 32 cm [below the 10 th centile] and length 49 cm with no dysmorphisms. She had a delayed cry at birth with an Apgar of 8 at 1 minute and 8 at 5 minutes. At 2 months of age, there was poor eye contact, delayed social smile, and poor neck control. There was a generalized hypotonia. Serum lactate, ammonia and Toxoplasma, Rubella, Cytomegalovirus and Herpes virus IgG and IgM were negative. Tandem Mass Spectroscopy was normal. **Interictal EEG** [Figure 2b] revealed a chaotic background admixed with frequent asynchronous high voltage slow waves, multifocal spikes and polyspikes suggestive of a hypsarrhythmia. **MRI** of brain [Figure 2c] was normal. **Genetic studies** [Figure 2d] Electrophoregram of the child revealed a **homozygous** mutation G > A at c. 1535 in exon 30 of WDR 62 gene. Patient received adrenocorticotrophic hormone,

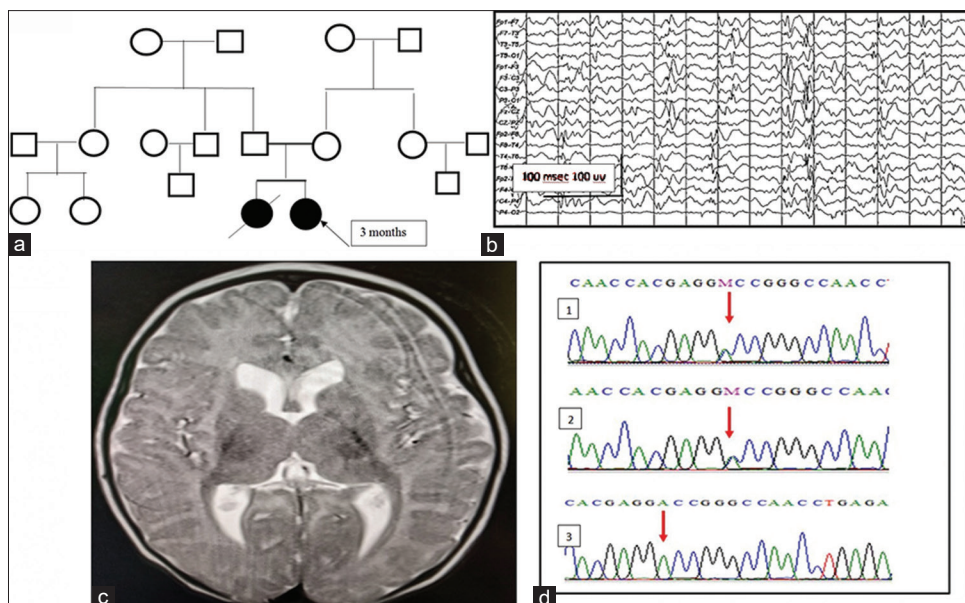


Figure 1: 1a. Case - 1: Pedigree chart of the family. 1b. Case - 1: Interictal EEG at 3 months - chaotic delta and theta background rhythm admixed with asynchronous high voltage slow waves, spikes and polyspikes. No sleep transients are seen. 1c. Case - 1: MRI Brain T2 sequence at 3 months is normal. 1d. Case - 1: [1 & 2] Whole exome sequencing revealed a heterozygous mutation at c. 3878 C > A in the father and the mother in exome 30 of the WDR 62 gene. [3] Electrophoregram of the affected child showed a homozygous mutation at c. 3878 C > A in exome 30 of the WDR 62 gene

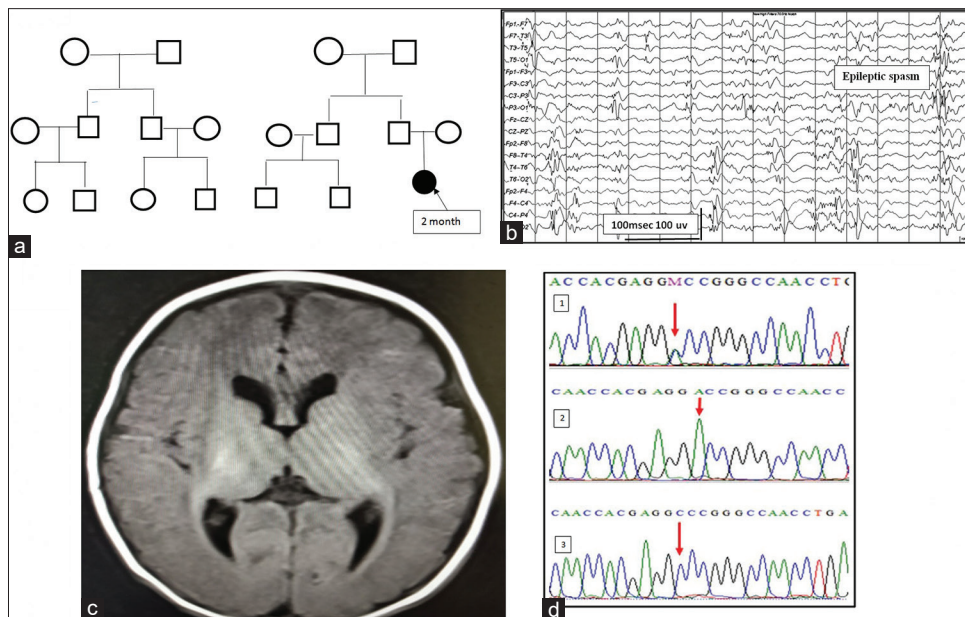


Figure 2: 2a. Case - 2: Pedigree chart of the family. 2b. Case - 2: Interictal EEG at 2 months - chaotic background with high voltage slow waves, multifocal spikes and polyspikes. Attenuation of the background activity follows an epileptic spasm. 2c. Case - 2: MRI Brain FLAIR at 2 months is normal. 2d. Case - 2: [1] Partial electrophoregram of the affected mother showing a heterozygous change from G > A at c. 1535 in exon 30 of WDR 62 gene. [2] Electrophoregram of the child showing a homozygous mutation G > A at c. 1535 in exon 30 of WDR 62 gene. [3] Father did not show any mutation

sodium valproate and clonazepam. At 6 months follow up, baby had infrequent spasms with global developmental delay. Electroencephalogram showed slowing of the background activity with occasional spikes.

Case 3 was an 8-month-old boy born, full-term, normal vaginal delivery to non-consanguineous parents [Figure 3a pedigree chart]. Apgar at birth was 8 at 1 minute and 10 at

5 minutes. Birth weight was 2300 gm, head circumference 33 cm [below the 10 th centile] and length 47 cm. Baby developed neonatal seizures and subsequently there were delayed motor milestones. At eight months of age, there were clusters of epileptic spasms with a global developmental delay. On examination there were no facial dysmorphisms, there was head lag with hypotonia and hyporeflexia. Serum

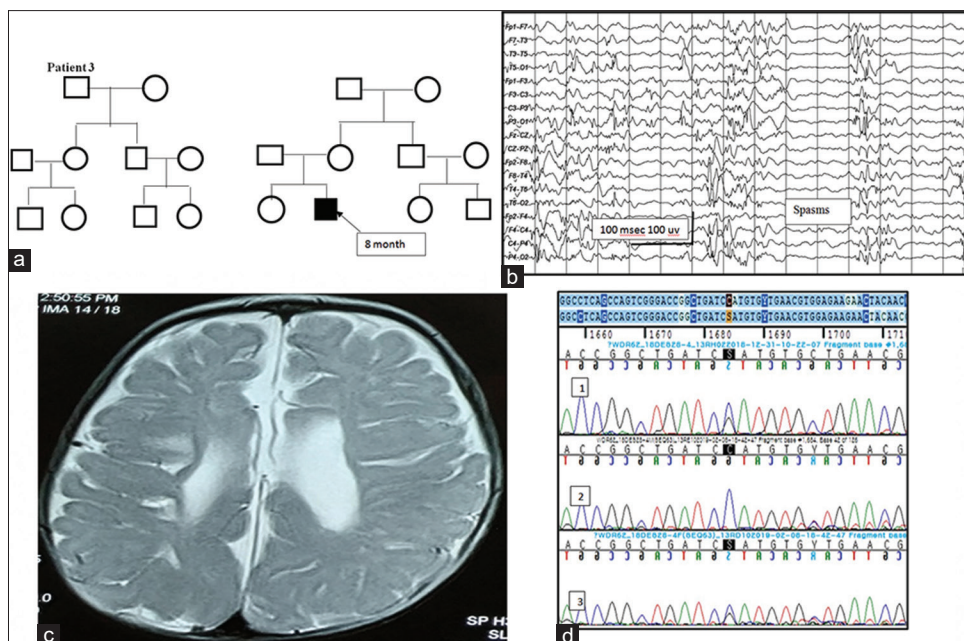


Figure 3: 3a. Case - 3: Pedigree chart of the family. 3b. Case - 3: Interictal EEG at 8 months of age - high voltage, asynchronous, background superimposed with multifocal spikes, polyspikes, and slow waves. 3c. Case - 3: MRI Brain T2 sequence at 8 months: Complete agenesis of the Corpus Callosum. 3d. Case - 3:[1] Electrophoregram of affected baby shows a heterozygous missense mutation C > G at c. 1684 on exon 13 of WDR 62 gene.[2] Electrophoregram of father is normal.[3] electrophoregram of the mother shows a heterozygous mutation C > G at c. 1684 on exon 13 of WDR 62 gene

ammonia, lactate, Toxoplasma, Rubella, Cytomegalovirus, and Herpes virus IgG and IgM were negative and Tandem Mass Spectroscopy was normal. Interictal EEG [Figure 3b] consisted of a high voltage, chaotic, asynchronous, disorganized background with multifocal spikes, polyspikes, and slow waves in both hemispheres. MRI of brain showed hypoplasia of the corpus callosum [Figure 3c]. Genetic studies [Figure 3d] Electrophoregram revealed a heterozygous mutation c. 1684 C > G in exome 13 of the WDR 62 gene in the baby. Patient received adrenocorticotrophic hormone, sodium valproate, and clonazepam. At 1 year follow up, there was psychomotor developmental delay with delayed speech and motor skills. A repeat electroencephalogram revealed a slow background rhythm with multifocal spikes.

Severe microcephaly is a term coined for a head circumference more than 3 standard deviations below the mean in addition to a height and weight at a similar percentile.^[1] Primary microcephaly is a static developmental anomaly with a decrease in the number of neurons at the time of birth while secondary microcephaly which develops after birth is a progressive neurodegenerative condition with a reduction in the dendritic processes and synaptic connections.^[2]

There are twenty-five MCPH genes expressed in the neuroepithelium of the fetal brain.^[3,8] A loss of DNA repair genes results in apoptosis of neurons during neurogenesis and a reduction in the cerebral cortical neurons during embryogenesis.^[3,4] The WDR 62 gene is located at the MCPH 2 locus at chromosome 19q13.12 with 32 functional exons and a genomic size of 50230 bp.^[4-6] WDR 62 is expressed in the neuronal precursor cells where it plays a role in cell

proliferation, spindle organization, neuronal migration, and regulation of neocortico genesis.^[5,6] Patients with the WDR 62 genetic mutation have an intellectual disability, language impairment, and epilepsy.^[4-6] The electroencephalographic findings in affected infants are that of hypersarrhythmia while in older children there is background slowing with multifocal spikes.^[7,8] MRI of the brain can be abnormal in cases of WDR 62 mutation.^[8] Treatment includes the management of hypersarrhythmia with adrenocorticotrophic hormone, anti-epileptics, and a ketogenic diet.^[8,9]

Autosomal recessive primary microcephaly is a static developmental abnormality affecting 0.14% of neonates. In the presence of unexplained microcephaly with classical clinical features, the general practice is to do a clinical exome sequencing of the parents to rule out known genetic mutations. Genetic counseling and carrier testing will help in reducing the incidence of MCPH in the affected population.

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Conflicts of interest

There are no conflicts of interest.

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