763. Evolving spectrum of COL4A1 related drug refractory epilepsy

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Introduction

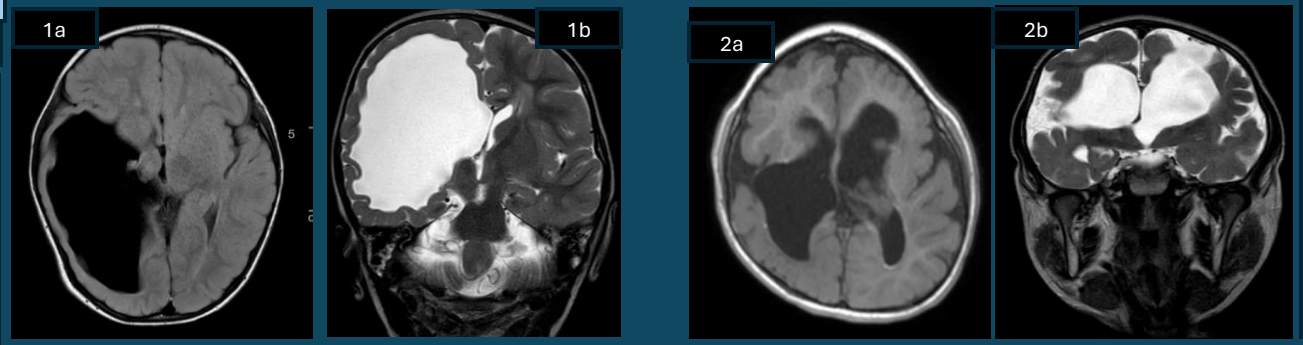
- COL4A1 mutations are rare genetic disorders with multisystem involvement and significant neurological involvement with continually evolving spectrum
- Most common phenotype: Focal seizures, frequently complicated by status epilepticus and DRE
- Epileptic spasm is present in more than 50% of the patients with this phenotype
- White matter changes are consistent finding on neuroimaging
- Neuroimaging changes can vary from florid abnormalities to subtle non-specific white matter signal changes or subtle ventricular enlargement
- Maternally inherited mutation may show worsening phenotype over generations
- Clear genotype-phenotype correlation is not well established

Methodology

- Children with heterozygous COL4A1/COL4A2 mutation attending epilepsy clinic were selected (n=8)
- Children with pathogenic variant (6/8) were selected to be included in this study
- Children with VUS (2/6): Excluded
- Clinical information as detailed in the clinic visit notes, Neuroimaging, EEGs were collected and tabulated for comparison

Results

- Mean age : 6.2 years (Range 3 to 8.6 years); M:F- 1:1
- Presenting symptom: Early infantile onset (3-6 months) in 5/6 children
  Late onset seizure (2.5 year) in 1/6 child with hemiparesis (GMFCS 2)
- Most common seizure type: Epileptic spasm (6/6)
- DRE: Most of the children (5/6)
- Epilepsy surgery : 1 child (ILAE I at last follow up).
- Common ophthalmological findings: Visual impairment and optic atrophy.
- Common neuroimaging findings: Bilateral (5/6), Porencephalic cyst, multiple punctate hemorrhage (4/6), open lip schizencephaly, subdural hematoma, white matter signal changes.
- Rare neuroimaging findings (1/6): Calcifications, dysplastic posterior fossa structures and decreased volume of basal ganglia and thalamus.
- EEG findings: Bilateral from beginning(5/6); Hypsarrhythmia (2/6), hemi-hypsarrhythmia (1/6); Multi focal discharges (3/6),
- Resolution of EEG abnormality of normal side (1/6- post surgery);
- Genetics: Diagnosis of COL4A1 mutation during infancy.
- Outcome: Passed away (1/6 @ 4 years)
  Significant disabilities (4/6)
  GMFCS2 (1/6)



Comparative neuroimaging features in the child with best outcome (1a, 1b) and the child who passed away (2a, 2b)
Right large porencephalic cyst communicating with right ventricle on axial FLAIR (1a) and T2 coronal sequence (1b). Axial T1 (2a) and Coronal T2 (2b) shows small head size and b/l focal porencephalic dilatation of the lateral ventricles. Overlying thin cortex appears slightly dysplastic with simplified gyral pattern.

Conclusion

- Early onset seizures suggest poor prognosis
- Patients with bilateral hemispheric involvement usually present early with seizures (within first 6 months)
- Imaging and initial EEG changes limited to one hemisphere suggest possible good surgical outcome
- Imaging features give clue for possible underlying etiology of COL4A1/2 diagnosis
- Timely intervention with epilepsy surgery in selected candidates can improve the quality of life.
- Posterior fossa structures and basal ganglia can be involved rarely.
- Early genetic diagnosis alerts the clinician to anticipate poor seizure control and need for aggressive approach to manage seizures.

References

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Acknowledgement

We express our gratitute to patients and their families for involving us in the care of these patients