Evaluation of genetic testing for children and young people with moderate to profound intellectual disability and epilepsy

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Background

The association between epilepsy and learning disabilities (LD) is well known. Several aetiological pathways contribute to the co-occurrence of these two conditions.
Large population-based studies have been conducted to understand the genetic aetiologies for early onset epilepsies and developmental disorders, but studies that include older children with LD who later develop epilepsy and have undergone genetic testing to unify their diagnosis are limited.

Objective

To evaluate the practice of genetic testing in older children and young people (3-18years old) in Special Needs Schools and STF units with LD and epilepsy and ascertain and identify the types of patients with LD and epilepsy, who would benefit from revisiting genetic testing.

Methods

Retrospective anonymised data was gathered from medical records of 59 children and young people (CYP) 3 -18years with moderate to profound LD and epilepsy. Data was gathered on the clinical phenotype and other variables including age, sex, level of LD, onset of epilepsy and co morbidities.

Established genetic diagnosis

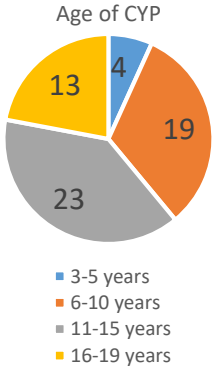
Male	Female
GRIN2A – 2 patients	SCN1A
Idic 15	MECP2 (Rett Syndrome)
SCL6A1 – 2patients	Atypical Rett
22q11 microdeletion	Alteration of PKNP gene
Tuberous sclerosis	Angelman syndrome
22q11microduplication – 2 patients	Wolf Hirschhorn syndrome
Angelman syndrome	Tuberous sclerosis
Ring chromosome 20	CDLK5
Chromosome 15q11.2 microdeletion	SLC2A1
Chromosome 15q 12-13 deletion	

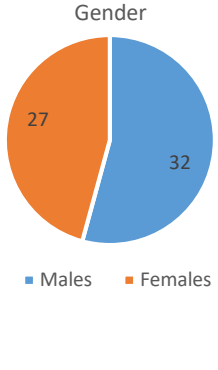
New genetic diagnosis

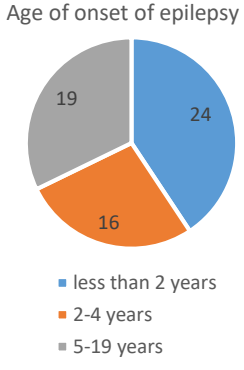
Patient	Current age	Sex	Level of ID	Other diagnoses	Age at onset of epilepsy	Epilepsy type/ Syndrome	Genetic abnormality	Age at genetic diagnosis
1	16yr 10m	M	Moderate	ADHD	8yr 0m	Absence Epilepsy	SLC6A1 mutation	14yr 4m
2	18yr 11m	M	Moderate	Nil	3yr 5m	Focal epilepsy with recurrent episodes of status & associated regression – Landau Kleffner syndrome	GRIN2A mutation	16yr 1m
3	13yr 0m	F	Moderate	Nil	2yr 6m	Generalised epilepsy. Developed CSWS at 9yr 4m	SCN1A mutation	10yr 0m
4	18yr 8m	F	Moderate	ASD	2yr 2m	Infrequent clusters of focal seizures	PCDH-19 mutation	11yr 10m
5	10yr 7m	M	Severe	Nil	4yr 3m	Absences and atonic seizures	RORB mutation (on WES)	8yr 1m
6	18yr 3m	F	Moderate	ADHD	3yr	Absence epilepsy	16p12.2 microdeletion	17 yr 3m
7	18yr	F	Moderate	ADHD	6yr	Focal epilepsy	GLRA2 variant on WES	17yr 1m
8	18yr 11m	M	Severe	Nil	13yr	Focal epilepsy	SCN8A	18yr 3m

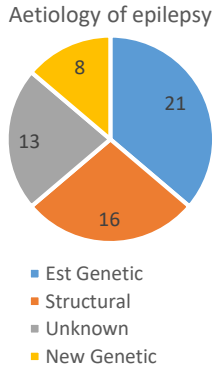
Results

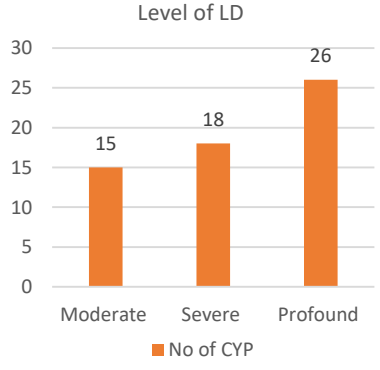
In the current study of 59 patients with both epilepsy and moderate to profound LD, 16 (27%) had a structural diagnosis; 21(37.5%) had an established genetic diagnosis; 8 (13.5%) received a new genetic diagnosis and 14 (24%) had unexplained LD and epilepsy. The diagnostic yield from testing children with no unifying diagnosis has been rewarding. The results came as a relief to the families, gave insight into the young person's diagnosis, facilitated genetic counselling, guided treatment and aided further assessments for the wider family. It also expands the phenotype of rare genetic abnormalities such as GLRA2 variant.











Conclusion

The study is highly relevant to current clinical practice with the changing and emerging landscape of genetic contributions in the aetiology of epilepsy and LD. It has provided insight into the current and previous practices of diagnostic assessments and into the different causes of LD and epilepsy. It has shown that genetic abnormalities are the most common cause of LD and co morbid epilepsy.
Most of the children who received a new diagnosis of genetic condition had only a moderate ID and did not develop their epilepsy in infancy and therefore were not obvious candidates for an epilepsy gene panel. It is vital that clinicians revisit the history and investigations in older children with learning disability and co-occurring epilepsy to explore whether they would benefit from the currently available genetic tests.