

## SHORT COMMUNICATION

# Importance of pedigree in patients with familial epilepsy and intellectual disability

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### ABSTRACT

In this study, we prospectively evaluated demographic characteristics, clinical findings and pedigree patterns in 70 patients with familial epilepsy and/or intellectual disability (ID)/global developmental delay (GDD) and/or motor retardation but without specific etiologic diagnosis to determine genetic inheritance patterns by using at least a three-generation pedigree analysis. Mean age of the patients was  $6.85 \pm 3.93$  years and male/female ratio was 1.50. There was consanguinity between the parents of 47 (67.1%) patients. Only epilepsy was diagnosed in 14 patients; only ID/GDD in 22; epilepsy and ID/GDD in 9 and epilepsy and ID/GDD and motor retardation in 25 patients. Genetic inheritance pattern was definitely determined in 60 (85.7%) patients, and most of the patients (61.4%) displayed autosomal recessive inheritance. Based on our findings, we suggest that a three-generation pedigree analysis should be obtained in all patients with familial neurological disorders, including epilepsy, ID/GDD and motor retardation, to optimise counselling, screening and diagnostic testing.

### KEYWORDS

Pedigree; Familial epilepsy; Intellectual disability.

### INTRODUCTION

A pedigree provides a graphic depiction of a family's structure and medical history. It is important when taking a pedigree to be systematic and use standard symbols and configurations [1]. A pedigree helps to identify patients and families who have an increased risk for genetic disorders [2]. The era of genomic medicine now has begun and will have an increasing effect on the daily care of common neurologic diseases [3]. Genetic risk analysis and interpretation have become central components for the modern clinical assessment, and a comprehensive family history analysis is essential for neurologists [4].

In this paper, we prospectively evaluated demographic characteristics, clinical findings and pedigree patterns in patients with familial epilepsy and/or intellectual disability (ID)/global developmental delay (GDD) and/or motor retardation to determine genetic inheritance patterns by using a comprehensive pedigree

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analysis in our region, in where frequency of consanguineous marriage is high, 34.4% [5].

## METHODS

Seventy patients with familial epilepsy and/or ID/GDD and/or motor retardation, but without specific etiologic diagnosis, were followed at the Department of Pediatric Neurology, Faculty of Medicine, Yüzüncü Yıl University and Necmettin Erbakan University, Turkey.

Familial epilepsy is defined as those cases, which lack specific clinical features or malformations, have at least one affected first-degree relative, and have no evidence for another causation [6]. Patients with familial epilepsy, ID/GDD with specific recognisable syndrome and specific diagnosis, such as cerebral palsy, congenital cytomegalovirus infection, congenital hypothyroidism, mitochondrial cytopathy, neurometabolic, neurodegenerative and lysosomal storage diseases, were excluded from the study.

Diagnosis of ID was made when intelligence quotient (IQ) testing revealed an IQ of less than 70, using Porteus Maze and Kent E-G-Y tests in patients who were cooperative and older than 6 years of age. Intelligence quotient was determined according to concurrent deficits or impairments in present adaptive functioning in different areas, mentioned in the literature, in patients who were non-cooperative and younger than 6 years of age [7,8].

GDD is defined as a significant delay in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal and activities of daily living [9]. The term GDD is reserved for children who are younger than 5 years, whereas the term ID is usually applied to older children for whom IQ testing is valid and reliable [9,10]. In our study, the term GDD was used for patients who were younger than 5 years.

General physical and neurological examination was performed in all patients. The patients were evaluated for personal and family history, pedigree construction, genetic inheritance patterns, demographic characteristics, clinical and

laboratory findings. At least a three-generation pedigree analysis was performed in all patients. The pedigrees were examined by a medical geneticist (SC). Based on patients' clinical findings, the cohort was classified as follows: patients with "only epilepsy," "only ID/GDD," "epilepsy and ID/GDD" and "epilepsy and ID/GDD and motor retardation."

Routine haematological and biochemical tests, thyroid hormone levels, tandem mass spectrophotometry, electroencephalography, visual evoked potential, auditory brainstem response and cranial magnetic resonance imaging were performed in all of the patients. Serum toxoplasmosis, rubella, cytomegalovirus, herpes infection markers, urinary organic acid level, X-ray, abdominal ultrasonography, cranial computerised tomography and karyotype analysis, were also performed in the required patients.

## RESULTS

A total of 70 patients with familial epilepsy and/or ID/GDD and/or motor retardation were studied. Mean age of the patients was  $6.85 \pm 3.93$  years (7 months–14 years). Forty-two (60%) were males and 28 (40%) were females (male/female ratio: 1.50). There was consanguinity between the parents of 47 (67.1%) patients. Clinical diagnosis of the patients was as follows: only epilepsy in 14 (generalised epilepsy in eight patients, partial epilepsy in five patients and partial epilepsy with secondary generalisation in one patient); only ID/GDD in 22 patients; epilepsy and ID/GDD in nine patients (generalised epilepsy in five patients, partial epilepsy in two patients and partial epilepsy with secondary generalisation in another two patients) and epilepsy and ID/GDD and motor retardation in 25 patients (generalised epilepsy in 22 patients and partial epilepsy in three patients). Based on pedigree analysis, genetic inheritance pattern was definitely determined in 60 (85.7%) patients and most of the patients (61.4%) showed autosomal recessive inheritance (Table 1).

## DISCUSSION

The key elements of the diagnostic evaluation in children with an ID/GDD are the developmental

and medical history, three-generation family history, dysmorphic examination, neurologic examination and judicious use of the laboratory and neuroimaging [11]. Van Karnebeek et al. [12] made etiologic diagnoses in 150 (54%) of 281 children with developmental delays or ID. One-third of these diagnoses were made on the basis of the history and examination alone [12]. In our study, we have evaluated demographic characteristics, clinical findings and pedigree patterns in patients with familial epilepsy and/or, ID/GDD and/or motor retardation by using at least a three-generation pedigree analysis. Patients with familial epilepsy and psychomotor retardation with specific etiologic diagnosis and children with isolated epilepsy, ID/GDD and motor retardation diagnosed by personal and family history and physical examination were not included in our study.

Single-gene causes have been diagnosed for a number of ID syndromes [13]. Mutations in X-linked genes may explain up to 10% of all cases of global developmental delay or ID [14]. Schaefer and Bodensteiner [15] state that the “association of ID and congenital malformations has long been recognised” and that “a necessary

component of the evaluation of the child with idiopathic ID is a comprehensive dysmorphic examination.” Several studies on ID suggest that the dysmorphic examination and syndrome recognition are the critical diagnostic modalities [11]. In our study, genetic inheritance pattern was definitely determined in 60 (85.7%) patients and was autosomal recessive in the most majority (61.4%) of patients.

Recent progress in the genetics of epilepsies may potentially provide important insights into biologic processes underlying epileptogenesis [16]. Most idiopathic epilepsies are oligogenic or polygenic disorders that show extreme clinical and etiological heterogeneity. Only a few monogenic idiopathic epilepsies are known; and although rare, they have contributed tremendously to our understanding of basic pathomechanisms in epileptogenesis [17]. The phenomenon of genetic heterogeneity implies that multiple genetic mutations may give rise to a similar phenotype. However, overlapping seizure features may lead to ambiguity when attempting to isolate a single phenotype [18]. Genetics has contributed to both rare and common epilepsies with or without ID [19]. Sugai et al. [20] evaluated 34 familial cases

**Table 1.** Inheritance patterns in the patients.

<b>Definite</b>	<b>n (%)</b>
Autosomal recessive	43 (61.4)
Autosomal dominant	6 (8.5)
Mitochondrial inheritance	5 (7.1)
Autosomal dominant with incomplete penetrance	3 (4.2)
X-linked recessive	2 (2.8)
Chromosomal abnormality	1 (1.4)
<b>Subtotal</b>	<b>60 (85.7)</b>
<b>Probable</b>	
Mitochondrial inheritance or autosomal recessive	2 (2.8)
Mitochondrial inheritance or chromosomal abnormality	2 (2.8)
Autosomal recessive or autosomal dominant or chromosomal abnormality	2 (2.8)
Autosomal dominant with incomplete penetrance or multifactorial inheritance	1 (1.4)
Autosomal dominant with incomplete penetrance or chromosomal abnormality	1 (1.4)
Autosomal recessive or mitochondrial inheritance or chromosomal abnormality	1 (1.4)
Autosomal recessive or X-linked recessive	1 (1.4)
<b>Subtotal</b>	<b>10 (14.3)</b>
<b>Total</b>	<b>70 (100)</b>

of West syndrome. They noted that the specific inheritance pattern was difficult to imagine in the majority of cases. In our study, only epilepsy was diagnosed in 14 patients; only ID/GDD in 22; epilepsy and ID/GDD in nine and epilepsy and ID/GDD and motor retardation in 25 patients.

## CONCLUSION

Our findings showed that the genetic inheritance pattern might be confidently determined in the majority (85.7%) of patients with familial epilepsy and/or ID/GDD by using a comprehensive pedigree analysis, and most patients (61.4%) displayed autosomal recessive inheritance. Based on our findings, we suggest that a three-generation pedigree analysis should be obtained in all patients with familial neurological disorders, including epilepsy, ID/GDD, and motor retardation, to optimise counselling, screening, and diagnostic testing.

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## CONFLICT OF INTERESTS

None.

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## ETHICS

The study was approved by the ethics committees of Erciyes University Faculty of Medicine and Necmettin Erbakan University Meram Medical Faculty. A written consent was received from the patients' parents.

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