What are the value of clinical factors for genetic testing utility in infantile developmental and epileptic encephalopathies ?

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OBJECTIVE

To identify the predictive value of evidence-based pre-defined clinical factors for genetic testing results in infantile developmental and epileptic encephalopathies (DEEs).

PATIENTS & METHODS

A comparative study was conducted with 166 patients diagnosed with infatile DEEs (< 3 years of age).

Two study groups were designed;

- **Group I (gene-named DEEs): 127 patients**
- **Group II (unknown-etiology DEEs with WES): 39 patients**

The following 16 independent predefined clinical factors in terms of genetic variant positivity in both groups were examined with univariate and multivariate analyses: *(1) gender, (2) type of seizure, (3) seizure frequency, (4) age at seizure onset (neonatal, <2 years), presence of (5) epileptic spasm (6) tonic seizure, (7) genetic stigma, (8) abnormal MRI, (9) special patterns on EEG, (10) abnormal metabolic screening, (11) febrile seizure, (12) status epilepticus, (13) family history of epilepsy, (14) comorbidity, (15) consanguinity, and (16) intellectual impairment* **(Table1).**

Table 1. Predefined clinical factors for genetic testing in patients with infantile DEEs

Clinical factors		Gen-named DEEs n (%) 127 (76.5)	Unknown DEEs with WES n (%) 39 (23.5)	p
Gender	Female	69 (54.3)	19 (48.7)	0.539
	Male	58 (45.7)	20 (51.3)	
Type of seizure	Focal	32 (25.5)	8 (21.1)	0.233
	Generalized	35 (27.6)	16 (42.1)	
	Multiple	60 (47.2)	14 (36.8)	
Presence of epileptic spasm		47 (37)	24 (61.5)	0.007
Presence of tonic seizure		32 (25.2)	11 (28.2)	0.708
Seizure onset	Neonatal period	19 (15.2)	5 (13.5)	0.800
	< 2 years	122 (97.6)	32 (86.5)	0.006
Seizure frequency	1-4/day	63 (52.5)	25 (64.1)	0.436
	1-4/week	26 (21.7)	5 (12.8)	
	1-4/month	25 (20.8)	6 (15.4)	
	1-4/year	6 (5)	3 (7.7)	
Special patterns on EEG		70 (57.4)	28 (87.5)	0.002
Abnormal MRI		52 (40.9)	20 (51.3)	0.255
Abnormal metabolic screening		15 (12.2)	-	0.024
History of febrile seizure		31 (24.4)	2 (5.1)	0.006
Presence of status epilepticus		58 (45.7)	12 (30.8)	0.099
Family history of epilepsy		31 (24.4)	6 (15.4)	0.236
Consanguinity		41 (41.4)	11 (31.4)	0.297
Presence of genetic stigma		63 (49.6)	25 (64.1)	0.113
Intellectual status	Normal	13 (10.2)	3 (7.9)	0.041
	Mild impairment	84 (66.1)	18 (47.4)	
	Severe impairment	30 (23.6)	17 (44.7)	
Presence of comorbidity		41 (32.3)	6 (15.4)	0.040

RESULTS

Among the clinical parameters, six predominant predictors were defined for a negative/positive result of genetic testing with univariate analysis**; (1) history of febrile seizure** (*predominant in gene-named DEEs*)**, (2) age at seizure onset < 2 years** *(more in gene-named DEEs)*, **(3) presence of epileptic spasm** *(prominent in unknown group)*, **(4) presence of special EEG pattern** (*prominent in unknown DEEs*)**, (5) comorbidity** *(more in gene-named DEEs)* , and **(6) intellectual status** *(severe impairment in gene-named DEEs*). However, all predictors except the history of febrile seizure were statistically significant in multivariate analysis (Table 2).

Table 2 . Univariate and multivariate analysis

Univariant analysis	HR	95 % CI	p
History of febrile seizure	5,974	1.361-26.226	***0.018***
Presence of epileptic spasm	2.723	1.301-5.702	***0.008***
Comorbidity	2.622	1.018-6.753	***0.046***
Age at seizure onset < 2 years	6.354	1.442-28.007	***0.016***
Intellectual status	2,644	1.209-5.786	***0.015***
Special EEG pattern	5,2	1.718-15.738	***0.004***
Multivariant analysis	**HR**	**95 % CI**	**p**
Presence of epileptic spasm	2.141	1.099-12.335	***0.035***
Comorbidity	8,745	2.471-30.949	***0.001***
Age at seizure onset < 2 years	7.773	5.548-1723,15	***0.002***
Intellectual status	3.850	1.284-11.545	***0.016***
Special EEG pattern	7.334	1.260-42-701	***0.002***

CONCLUSIONS

This study revealed six predominant predictors for genetic testing in the presented infantile DEEs cohort. Each clinical factor might be indicative of a well-defined electroclinical syndrome or a gene named DEEs. However, the presence of more special patterns on EEG and a high incidence of infantile spam-type seizures in the WES-negative DEEs group indicate the necessity to further genetic diagnostic investigation (reanalysis of WES, WGS, RNA sequencing, reverse fenotyping, and genomic mapping analysis) in those patients.

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