National Registry of Dravet's Syndrome and other Syndromes correlated with genes SCN1A and PCDH19

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01 INTRODUCTION

Patient Registries have been recognized by the European Community as one of the priorities of strategic intervention in the Rare Illnesses sector. [1] These constitutes an essential instrument for improving the understanding of the illness through the systematic and continual registration of data for basic clinical and epidemiological researches, with the aim of developing new therapeutic solutions and programming social-health services in order to improve patients' and their families quality of life. The Dravet Italy Non-profit Association (http://dravetitalia.org/) has promoted the development of the "National Registry of Dravet Syndrome and other Syndromes related to mutations on SCN1A and PCDH19 genes"

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02 OBJECTIVES

Dravet Syndrome (DS), also known as severe myoclonic epilepsy of infancy , is a rare form of epilepsy associated with neurological developmental disorders. The incidence of the disease has been estimated between 1/20,000 and 1/40,000, with a greater frequency in males than in females; symptoms appear in the first year of life with recurrent epileptic seizures, often triggered by fever. There is an ample spectrum of clinical variability associated with SCN1A disorder. The purpose of the Registry is to provide the scientific community, sanitary authorities, industry, patients and their families, a valid and up-to-date source of data concerning DS and related syndromes. Moreover the registry will act as a constant reference promoting the active interaction of all research and sanitary structures present in the country, in support of more adequate strategies for diagnosis, therapy and care.

03 METHODS

The working group, after having identified the main aims of the registry, elaborated its structure, establishing 11 headings: Anagraphic Data; Genetic Investigations; Family History, Personal History ; Seizures Semeiology at Onset; Seizures at Follow-up; Neurological Follow-up; Neuropsychological Data, Treatments ; EEG and other exams; Adverse and Exceptional Events, Disability and Health Care Costs.
An electronic database has been elaborated in order to collect the information retrospectively and also prospectively. For those patients for whom some information is missing an historical form has been realized.

05 EXPECTED RESULTS

- Acquisition of clinical, genetic and epidemiological data regarding these syndromes
- Evaluation of pharmacological treatments efficacy
- Evaluation of epileptic seizures, neurological, cognitive and behavioural outcome
- Evaluation of comorbidities and adverse events
- Promotion of further correlation between genotypes and phenotypes studies.

06 CONCLUSIONS

The Registry could represent an important instrument for the systematization of data regarding DS and related syndromes, in order to improve understanding of the illness and promote related research. Reports and up-to-date graphics of cumulative data which could be essential to promote the knowledge of the illness and its social and economic impact will be made available to all interested parties, for promoting and sustaining scientific research, with the aim of discovering innovative therapeutic options for the management of DS and correlated syndromes. Starting from these preliminary results we would like to expand the use of the registry in Europe.

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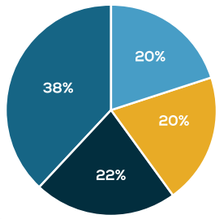
AGE LAST VISIT

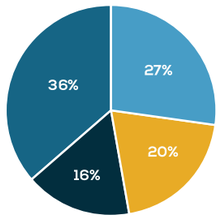
The age at last visit is heterogeneous with a significant number of adults in DS group and in OS group.

AGE	N° PATIENTS DRAVET SYNDROME	N° PATIENTS OTHER SYNDROME SCN1A GENE RELATED	N° PATIENTS PCDH19
from birth to 5 years	15	12	2
from 6 to 10 years	15	9	5
from 11 to 18 years	16	7	3
from 19 years	28	16	1
TOTAL	74	44	11

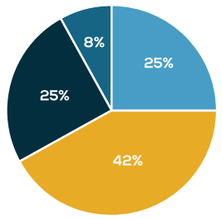
DRAVET SYNDROME



OTHER SYNDROME SCN1A GENE RELATED



PCDH19

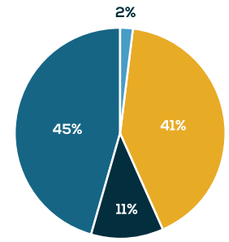


GENETIC EXAMS AND RESULTS

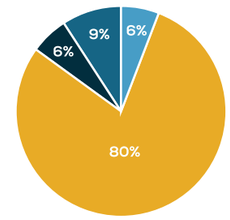
Reports the type of genetic findings. Most cases with DS have SCN1a mutation or deletion (82/87). While missence mutations are predominating in OS and PCDH19 groups, truncating mutations are present in nearly half of DS cases.

AGE	N° PATIENTS DRAVET SYNDROME	N° PATIENTS OTHER SYNDROME SCN1A GENE RELATED	N° PATIENTS PCDH19
MISSENSE MUTATION	34	43	12
TRUNCATING MUTATION	37	5	4
UNCLEAR EFFECT ON THE PROTEIN	9	3	0
DELETION	2	3	2
TOTAL	82	54	18

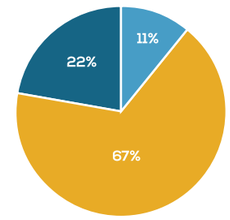
DRAVET SYNDROME



OTHER SYNDROME SCN1A GENE RELATED



PCDH19

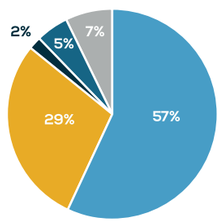


SEIZURES ONSET

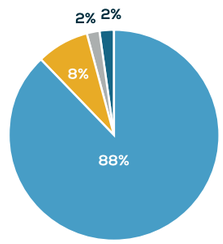
The ictal semeiology at onset shows that most subject with DS present unilateral seizures, instead subjects with OS and PCDH19 have convulsive seizures and /or focal seizures. The type of seizures are more variable in DS and in PCDH19 than in OS . Moreover unilateral seizures are frequent in DS while focal seizures are very frequent in PCDH19.

TYPE SEIZURES ONSET	N° PATIENTS DRAVET SYNDROME	N° PATIENTS OTHER SYNDROME SCN1A GENE RELATED	N° PATIENTS PCDH19
CONVULSIVE GENERALIZED OR SEC. GENERALIZED	50	43	8
UNILATERAL CONVULSIVE	25	4	0
IMPAIPMENT/LOSS CONTACT WITHOUT MOTOR MANIFESTATIONS	2	0	2
MYOCLONUS	4	1	1
FOCAL	6	1	7
TOTAL	87	49	18

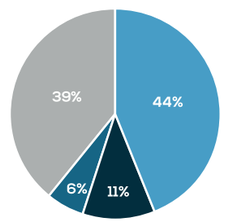
DRAVET SYNDROME



OTHER SYNDROME SCN1A GENE RELATED



PCDH19



TYPE SEIZURE AT LAST VISIT

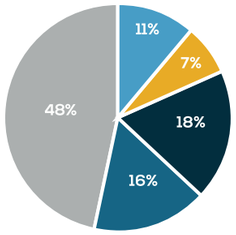
Even at follow up the seizures type are more variable in DS. On the contrary generalized seizures are predominating in OS and focal seizures are frequently in clusters in PCDH19.

TYPE SEIZURES AT ONCET	DRAVET SYNDROME		OTHER SYNDROME SCN1A GENE RELATED		PCDH19	
	N° PATIENTS	74 PATIENTS %	N° PATIENTS	44 PATIENTS %	N° PATIENTS	11 PATIENTS %
ABSENCES	15	20%	1	2%	0	0%
GENERALIZED TONIC CLONIC	43	58%	14	32%	4	9%
SEIZURE UNILATER	8	11%	1	2%	0	0%
FOCAL	22	30%	5	11%	8	18%
MYOCLONUS	11	15%	2	5%	1	9%
EPYLEPTIC STATUS	6	8%	2	5%	0	0%
CLUSTER	9	12%	0	0%	6	55%

COGNITIVE LEVEL IN RELATION AT THE AGE

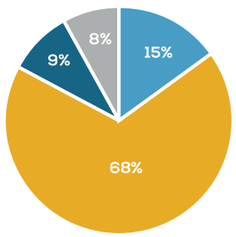
Cognitive outcome: cognitive impairment is more frequent in DS and PCDH19 than in OS and particularly in DS increases with age.
In PCDH19 cases the cognitive outcome is more variable than in DS with a significant number of subjects without impairment.

DRAVET SYNDROME



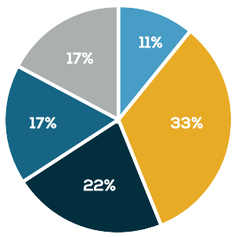
COGNITIVE LEVEL	AGE 0-5	AGE 6-10	AGE 11-18	AGE FROM 19	TOTAL
NORMAL	6	0	0	0	6
BORDER LINE	3	4	2	0	9
MILD IMPARIMENT	3	3	5	3	14
MODERATE IMPARIMENT	4	12	11	13	40
SEVERE IMPARIMENT	1	3	2	9	15
TOTAL	17	22	20	25	84

OTHER SYNDROME GENE SCN1A RELATED



COGNITIVE LEVEL	AGE 0-5	AGE 6-10	AGE 11-18	AGE FROM 19	TOTAL
NORMAL	8	8	4	16	36
BORDER LINE	3	2	3	0	8
MILD IMPARIMENT	2	2	1	0	5
MODERATE IMPARIMENT	2	0	2	0	4
SEVERE IMPARIMENT	0	0	0	0	0
TOTAL	15	12	10	16	53

PCDH19

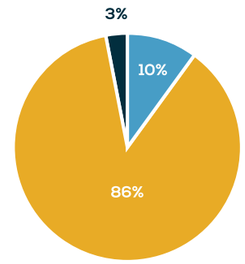


COGNITIVE LEVEL	AGE 0-5	AGE 6-10	AGE 11-18	AGE FROM 19	TOTAL
NORMAL	2	4	0	0	6
BORDER LINE	1	0	1	0	2
MILD IMPARIMENT	2	0	1	0	3
MODERATE IMPARIMENT	2	0	1	0	3
SEVERE IMPARIMENT	0	1	3	0	4
TOTAL	7	5	6	0	18

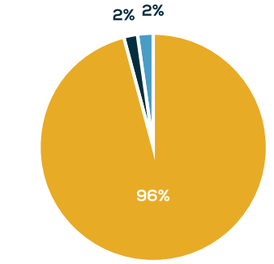
AUTISTIC SPECTRUM

Autistic Spectrum disorders are predominant in PCDH19 subjects and are exceptional in OS.

DRAVET SYNDROME

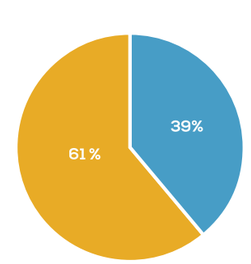


OTHER SYNDROME SCN1A GENE RELATED



OTHER EPILEPSIES	3
FOCAL EPILEPSY	3
GEFS/FEBRILE SEIZURES	39
NOT SEIZURES	4
EPILEPTIC ENCEPHALOPATHIES	3
GEFS/FEBRILE SEIZURES	1
FOCAL EPILEPSY	1

PCDH19

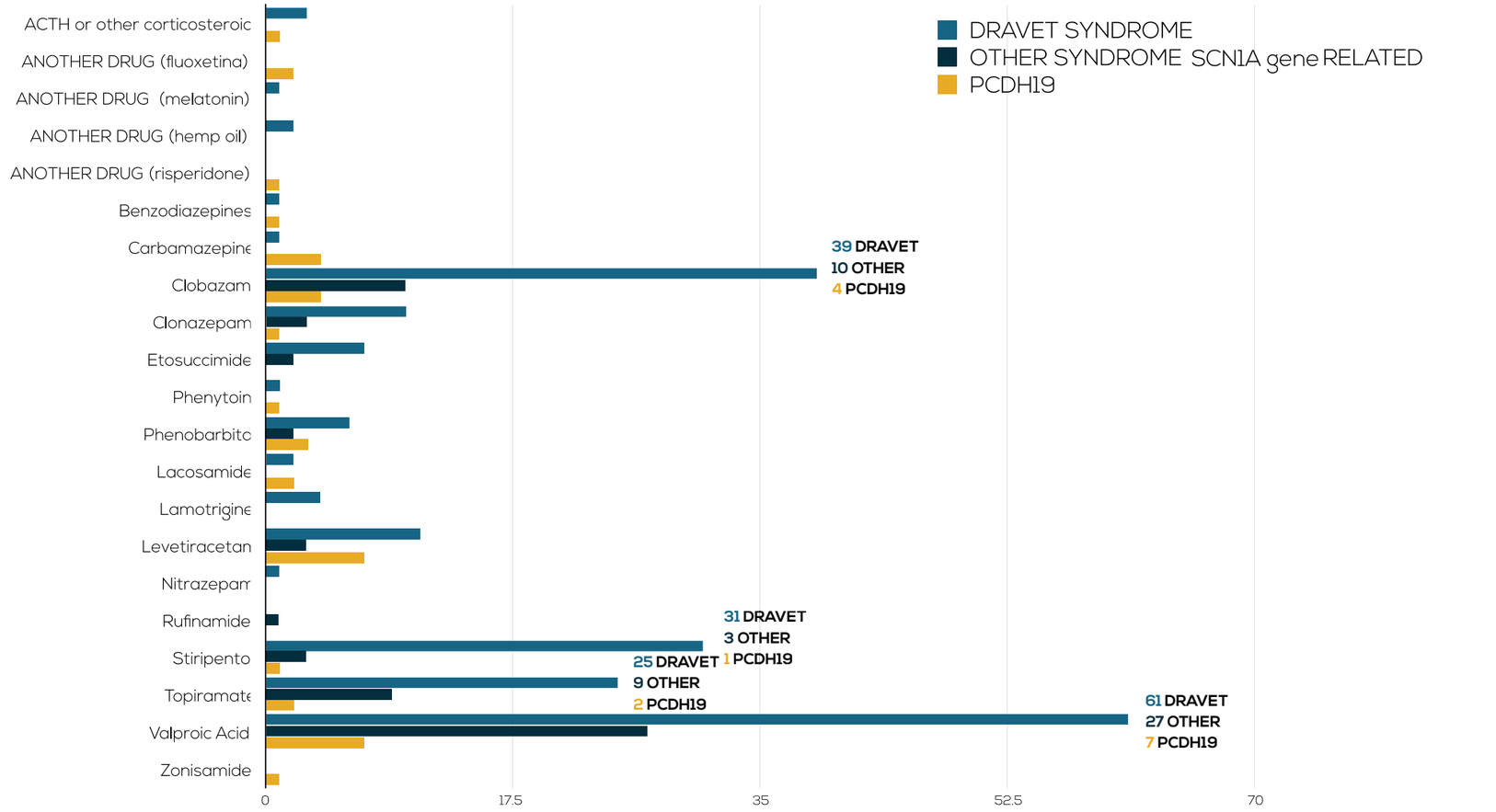


WITH SEIZURE	7
WITHOUT SEIZURE	0
WITH SEIZURE	10
WITHOUT SEIZURE	1

AUTISTIC SPETTRUM	N° PATIENTS DRAVET SYNDROME	N° PATIENTS OTHER SYNDROME SCN1A GENE RELATED	N° PATIENTS PCDH19
YES	9	1	7
NOT	75	52	11
N.D.	3	1	0
TOTAL	87	54	18

CURRENT THERAPY

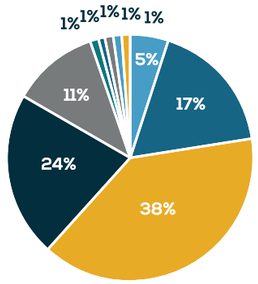
The most frequently used drug is valproate often associated with clobazam in DS and OS and with stiripentol in DS. Levetiracetam is frequently used in PCDH19 patients and topiramate in DS and OS. While monotherapy is efficient in half of the OS cases and in a third of PCDH19 cases, polytherapy with multiple drugs is very frequent in DS cases.



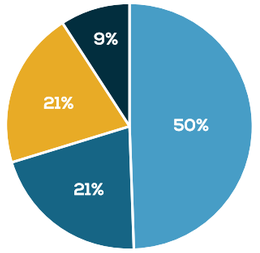
ANALYSIS OF PATIENTS FOR MONO AND POLY THERAPY

N° DRUGS CURRENT THERAPIES	1 DRUG	2 DRUGS	3 DRUGS	4 DRUGS	5 DRUGS	6 DRUGS	7 DRUGS	8 DRUGS	10 DRUGS	14 DRUGS	15 DRUGS	TOT
N° PATIENTS DRAVET SYNDROME	4	14	32	20	9	1	1	1	1	0	1	84
N° PATIENTS OTHER SYNDROME SCN1A GENE RELATED	17	7	7	3	0	0	0	0	0	0	0	34
PCDH19	5	5	3	2	0	0	1	0	0	1	1	18

DRAVET SYNDROME



OTHER SYNDROME SCN1A GENE RELATED



PCDH19