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A validation study of the clinical diagnosis of Dup15q syndrome: Which symptoms matter most?

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ABSTRACT

Purpose: Dup15q syndrome is a rare genetic disease with a fairly nonspecific phenotype, clinical heterogeneity, and a wide spectrum of severity. However, no formal characterization has been attempted to select clusters of symptoms, signs and instrumental tests, to be used in the differential diagnosis with other neurodevelopmental disorders. Thus, our purpose was to identify symptoms, signs and instrumental findings, singly or in various combinations, favoring the early diagnosis of the Dup15q syndrome and the indication for genetic testing.
Methods: 25 patients with Dup15q syndrome and 25 age and sex matched controls with other neurodevelopmental disorders were the study population. Patients' history, clinical and instrumental assessment were examined by five expert child neurologists blind to the genetic diagnosis. Each rater was asked to make the diagnosis in three subsequent steps: 1. Revision of the medical records; 2. Examination of the videorecorded clinical findings; 3. Assessment of the instrumental tests. Inter-rater agreement was measured with the Kendall's coefficient of concordance) and the Kappa statistic. Sensitivity, specificity and predictive values for symptoms, signs and instrumental findings, singly or in various combinations, were measured.
Results: The Kendall's coefficient for the diagnosis of Dup15q syndrome was 0.43 at step 1 was 0.43, at step 2 was 0.42, at step 3. Patients with past feeding difficulties, hypotonia during the neonatal period, and epilepsy had > 80 % probability of having the Dup15q syndrome.
Conclusion: Feeding difficulties, hypotonia and epilepsy, though unspecific, can be used as signals of Dup15q syndrome and focused search of genetic abnormalities.

1. Introduction

The Dup15q syndrome has received little attention because of its rarity, the fairly nonspecific phenotype, the clinical heterogeneity, and the wide spectrum of severity. Along with developmental delay, autism spectrum disorder (ASD) and epilepsy are predominant components of the clinical picture. In a retrospective cohort of 30 unrelated patients [1], 77 % of cases met the criteria for developmental delay, while 74 % had a diagnosis of ASD. In a prospective study of children with Dup15q syndrome [2], ASD was diagnosed in 9/9 patients with maternally derived duplications and in 2/4 patients with paternally derived duplications. Epilepsy often develops early in infancy, with rates of 63 % in idic(15) and 16 % in interstitial duplications [3].

Although attempts have been made to identify common clinical features (hypotonia, developmental delay/intellectual disability, ASD, and epilepsy) [4], no formal characterization of the phenotype has been attempted with the intent to select clusters of symptoms, signs and instrumental tests, which could be used in the differential diagnosis

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with other neurodevelopmental disorders characterized by mental retardation. intellectual disability, epilepsy, and abnormal behavior [5].

Although routine clinical genetic screening is now recommended for the etiological evaluation of all children with new diagnoses of global developmental delay, intellectual disability, or autism spectrum disorder [6,7], genetic testing might not be affordable or even accessible on a widespread basis, especially in developing countries.

The diagnostic contribution of individual symptoms and/or signs and their combinations not only favors an early diagnosis of the Dup15q syndrome, but also helps defining any genotype-phenotype correlation and could be a valuable reference for epidemiological studies.

We aimed to validate the diagnosis made by child/pediatric neurologists based on symptoms, signs and instrumental findings comparing a cohort of patients of differing age and sex with confirmed diagnosis of Dup15q syndrome to patients usually considered in the differential diagnosis as having intellectual disability, functional impairment, and behavioral abnormalities in various combinations. The purpose of this study was to identify individual symptoms/signs or clusters of symptoms/signs that could be used as signals of Dup15q syndrome in settings where genetic testing might not be accessible or affordable.

Specific aims of the study include:

1 The identification of symptoms, signs and instrumental findings, singly or in various combinations, favoring the early diagnosis of the Dup15q syndrome;
2 The characterization of the diagnosis of the Dup15q syndrome, based on the most distinctive phenotype in the absence of genetic testing.

The research question to be addressed is that there are symptoms/signs that, although not specific, if properly combined, might lead clinicians to think of this rare syndrome.

2. Methods

The study population consisted of 25 patients of all ages and either sex with Dup15q syndrome (the cases) and 25 patients (the controls) with other diseases involved in the differential diagnosis. Cases (21 Invdup15 and 4 Intdup15) were consecutively enrolled from two of the participating institutions (Medea, Oasi) between January 2015 and December 2017. Controls were matched by age (± 1 year) and sex. These include other neurodevelopmental disorders characterized by intellectual disability, autism, abnormal behavior, functional impairment. The sample included Angelman syndrome (7 cases), ASD (3), Rett syndrome (2), Dravet syndrome (2), FOXG1 syndrome (2), epileptic encephalopathy (2), Pitt-Hopkins syndrome (2), pervasive developmental disorder (2), X-fragile syndrome (1), cryptogenic epilepsy with cognitive delay (1), and intellectual disability with language disorder (1). These clinical conditions cover a wide spectrum of diseases, some of them confirmed by genetic tests and others by extensive follow-up accompanied by history, clinical investigation and imaging studies.

The diagnosis of each clinical condition (the gold standard) was the one made by the referring child neurologist and was based on the results of clinical and instrumental tests (including genetic tests). After releasing a written informed consent, the family members (or other legal representatives) of eligible cases and controls permitted the diagnostic assessment of the affected individuals, including the accession to the patients' medical records. For each individual included in the study, an accurate history was taken from a key informant. The patient underwent a full clinical investigation (including the neurological examination, the assessment of spontaneous behavior and his/her basic interactions with the examiner). History and clinical assessment were video-recorded in the caring physician's office.

Video-recordings and all the material included in the patients' medical records (except for the results of the genetic tests) were examined by five expert child neurologists chosen among those routinely involved in the management of neurodevelopmental disorders. The experts (the raters) were blind to the diagnosis. Each rater was asked to indicate for each diagnosis, the degree of certainty (as definitely yes, probable, uncertain or definitely no) in three subsequent steps, the first after reviewing the medical records (deprived of the information obtained from the instrumental tests), the second after examining the video-recordings, and the third after examining the results of the instrumental tests. At each step raters had also to indicate if pre-specified symptoms, signs and instrumental findings were present, absent or not identifiable/unavailable. At each step, a separate section of an e-CRF was filled. The study was approved by the Ethics committees of the involved centers.

2.1. Statistical methods and data analysis

The inter-rater agreement for Dup15p syndrome and other clinical conditions was tested using the Kendall's coefficient of concordance (W). The degree of diagnostic certainty for Dup15p syndrome was also tested in cases and controls separately, using frequencies and percentages. Missing data were coded as uncertain. The inter-rater agreement was tested for each symptom, sign and instrumental finding separately, using Kendall's W for ordinal variables and Fleiss's Kappa for categorical variables. Missing data were coded as not identifiable/unavailable. Kendall's W and Fleiss' K take values from 0 (no agreement) to 1 (perfect agreement). Symptoms, signs and instrumental findings with Kendall's W no less than 0.6 were subsequently evaluated in terms of AUC (Area Under the receiver operating characteristics [ROC] Curve). AUC values range from 0.5 (no discrimination) to 1 (perfect discrimination). Univariable and multivariable logistic regression models were used to evaluate the discriminant ability of signs, symptoms and instrumental findings, alone and in different combinations. The best combination was selected through two different procedures:

1) stepwise automatic selection based on level of significance of variables included in the model;
2) manual selection of variables, starting from the variable with the highest AUC, and adding one by one all other variables, maintaining in the model only those leading to a significant increase of the AUC. Sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) corresponding to the best cut-off probability of being classified as a case (Dup15p) or a control (other clinical conditions) were also calculated from each model. The best cut-off probability was selected as the probability level leading to the maximum percentage of correctly classified observations.

Each rater examined charts and videos of all cases and all controls, giving a total of 250 observations (125 + 125). Sample size was planned to 25 cases and 25 controls because the number of available cases could not exceed 25.

3. Results

A total of 50 patients were enrolled, 25 with a diagnosis of Dup15q syndrome and 25 with other neurodevelopmental disorders. The genetic diagnosis of Dup15p cases and the diagnoses of the controls is illustrated in the Appendix. The genetic diagnosis of dup15q individuals [21 idic15 or (invdup15), 4 in. dup(15)] and the diagnoses of the controls are illustrated in the Appendix. The sample includes 20 female and 30 males aged 3–43 years (median 11; interquartile range IQR 5–13). Supplementary Table S1 shows the general characteristics of the sample. Birth weight, length and head circumference are presented in Supplementary Table S2 for females and males, with reference to the WHO standards (who.int/childgrowth/en). No differences were found between cases and controls. No adverse events were reported during the

Table 1
Diagnostic accuracy in cases and controls at each subsequent step.

Dup15p diagnosis	Step 1				Step2				Step 3			
	Cases		Controls		Cases		Controls		Cases		Controls	
	n	%	n	%	n	%	n	%	n	%	n	%
No	40	32.0	68	54.4	40	32.0	62	49.6	45	36.0	66	52.8
Uncertain	21	16.8	25	20.0	23	18.4	26	20.8	20	16.0	26	20.8
Probable	55	44.0	29	23.2	55	44.0	33	26.4	47	37.6	27	21.6
Certain	9	7.2	3	2.4	7	5.6	4	3.2	13	10.4	6	4.8

video-recorded interviews.

3.1. Inter-rater agreement on the diagnosis

Table 1 shows Kendall's W for all diagnostic categories. The concordance for the diagnosis of Dup15q syndrome, measured by Kendall's W was 0.43 at step 1; 0.42 at step 2 and 0.37 at step 3. The corresponding values in the controls are illustrated in Supplementary Table S3.

3.2. Degree of diagnostic accuracy

The degree of diagnostic accuracy for Dup15q syndrome is reported in Table 1 for cases and controls and for each step, separately. Accuracy (No, Uncertain, Probable, Certain) was reported for all raters among cases (125 observations) and controls (125 observations) separately. Each patient was considered as many times as the number of raters. Considering the single answers, the No answers in the control group decreased from 54.4% to 49.6% from step 1 to step 2 and increased to 52.8% at step 3; the Uncertain answers remained almost the same at each step; the Probable answers decreased from 23.2% at step 1 to 21.6 at step 3; the Certain answers increased from 2.4% to 4.8%. Among cases, the No answers increased from 32.0% to 36.0%; the Uncertain answers were stable; Probable answers remained stable at step 1 (44.0%) and 2 (44.0%) and decreased at step 3 (37.6%); the Certain answers decreased from 7.2% (step 1) to 5.6% (step 2) and then increased to10.4% at step 3.

3.3. Inter-rater agreement for signs, symptoms and instrumental examinations

Inter-rater agreement for signs, symptoms and instrumental examinations is reported for each step in Supplementary Table S4. Variables reaching the pre-set threshold (0.6) for the concordance coefficient (W or K) included feeding difficulties in the newborn period, standing, walking, speech, anteverted nares, obesity, hypotonia, hypotonia present at visit, developmental delay, mental retardation, epilepsy, infantile spasms, focal seizures, spike-slow waves, polyspike-slow waves.

3.4. Analysis of the discriminating ability of signs, symptoms and instrumental examinations

The discriminating ability of signs, symptoms and instrumental examinations was evaluated for variables with a good level of inter-rater agreement (W or K coefficient no less than 0.6).

For those variables, frequency and percentages of cases and controls in which raters judged each sign, symptom or instrumental finding as present or unknown are shown in Table 2.

Table 3 shows the AUC values for signs, symptoms and instrumental examinations, alone and in different combinations, along with SE, SP, PPV and NPV obtained for the best selected cut-off probability.

Stepwise selection and manual selection of variables to be included in the final model provided the same combinations of signs, symptoms and instrumental findings. The final selected model is highlighted in bold in Table 3.

Fig. 1 shows the comparison of ROC curves (with AUC values) for the model (model 1) including only the variable with the best AUC value (feeding difficulties during newborn period) and for all models showing a significant increase of the AUC, as compared to model 1.

4. Discussion

In the absence of confirmatory genetic tests, Dup15q syndrome does not present clinical, electrophysiological and imaging findings supporting the diagnosis. The results of our study show that inter-rater agreement and diagnostic accuracy are at best moderate when comparing patients with Dup15q syndrome and other neurodevelopmental disorders and do not increase when the information from the medical records is supplemented by the videorecordings of the patients and by the results of the instrumental tests (EEG, imaging). Moderate diagnostic accuracy and moderate inter-rater agreement can be attributed to the nonspecific symptoms, signs and instrumental findings, which may be difficult to detect if not recordable or left to the results of a short-lasting video. In the absence of diagnostic phenotypes, the majority of the symptoms and signs can be found in any of the neurodevelopmental disorders, including Dup15q syndrome. However, sensitivity is fairly high in the presence of obesity, epilepsy and, to a lesser extent, hypotonia. Epilepsy and hypotonia are part of the disease phenotype [4,8]. Battaglia [8] suggested that clinicians should suspect this syndrome in any infant with early central hypotonia, minor dysmorphic features, developmental delay, autism or autistic-like behaviour, and who subsequently develops hard to control seizures/epilepsy. In contrast, obesity is not contemplated in the Dup15p phenotype which focuses on neurological and psychiatric symptoms and signs.

The inter-rater agreement on the EEG findings is at best moderate, which indicates that medical history does not necessarily rely on the results of neurophysiological tests, as the interpretation of the tracings can vary even in the hands of expert clinicians. Likewise, imaging findings may have been variously interpreted by the raters because they are not strictly associated with a given neurodevelopmental disease.

Although, with few exceptions, the diagnostic value of each symptom, sign or instrumental finding is not high, combinations of selected clinical findings can help the differential diagnosis. In this regard, the presence of feeding difficulties in the newborn period, hypotonia, history of infantile spasms and the occurrence of focal seizures, when combined, show the best positive predictive value. This suggests that a patient with epilepsy associated with past feeding difficulties and hypotonia observed during the neonatal period has a more than 80 % probability of being affected by Dup15q syndrome.

Other clinical features that are present in the definition of Dup15q syndrome are fairly inaccurate and unreliable. Abnormal behavior compatible with ASD was not found to predict Dup15q syndrome. A likely explanation is that while a large proportion of children with Dup15q syndrome meet the diagnostic criteria for ASD, there are distinctive behavioral and developmental features in this cohort that can

Table 2
Signs, symptoms and instrumental findings with inter-rater agreement ≥ 0.6.

Variable	Cases			Controls		
	n (%) unknown	n positive	% positive	n (%) unknown	n positive	% positive
Step 1						
Feeding difficulties newborn period	25 (20)	70	56.0	29 (23)	31	24.8
Standing	10 (8)	102	81.6	6 (5)	109	87.2
Walking	4 (3)	99	79.2	3 (2)	112	89.6
Speech	5 (4)	51	40.8	6 (5)	59	47.2
Epilepsy	9 (7)	91	72.8	6 (5)	85	68.0
Infantile spasms	28 (22)	36	28.8	36 (29)	11	8.8
Focalseizures	28 (22)	69	55.2	38 (30)	50	40.0
Step 2						
Antevertednares	2 (2)	11	8.8	2 (2)	4	3.2
Obesity	2 (2)	8	6.4	0 (0)	21	16.8
Hypotonia	24 (19)	69	55.2	19 (15)	47	37.6
Hypotonia present at visit	25 (20)	60	48.0	20 (16)	49	39.2
Developmental delay	0 (0)	50	40.0	0 (0)	51	40.8
Mental retardation	0 (0)	64	51.2	0 (0)	64	51.2
Step 3						
Spike-slow waves	20 (16)	64	51.2	22 (18)	65	52.0
Polyspike-slow waves	20 (16)	49	39.2	23 (18)	44	35.2

be captured only by an accurate assessment of social communication and adaptive functions [9,10]. In addition, in line with a published report [11], Dup15q syndrome does not have a distinct electroclinical phenotype. Developmental delay and mental retardation are not distinctive features when comparing cases and controls and autistic behavior is present in similar proportions. These same signs are perhaps nonspecific and, based on the information made available to the raters, subjected to variable interpretation even by experienced child neurologists.

The study has strengths and limitations. This is the first study investigating the validity and reliability of clinical and instrumental findings considered for the differential diagnosis between Dup15q syndrome and other neurodevelopmental disorders. However, the external validity of the results depends on the type of controls selected for the differential diagnosis. We do not know if the results would have been the same if the controls were affected by other clinical conditions. A second limitation is represented by the raters chosen for the validation of the diagnosis. These raters were selected as being among the most experienced child neurologists in the country. We cannot however exclude that different results might have been obtained if other raters, perhaps less experienced, were involved. A third limitation is the small number of cases and controls, which might have affected the precision of our estimates.

5. Conclusion

Feeding difficulties, hypotonia and epilepsy, though unspecific when taken singly, if combined can be used as signals of Dup15q syndrome. Our findings can be useful information to be delivered to the clinicians for a correct diagnosis of Dup15q syndrome and help them making a more focused search of the genetic abnormalities that are part of the genotype/phenotype picture. The combination of feeding difficulties, hypotonia and epilepsy cannot be, however, used as a signal of Dup15q syndrome for case ascertainment in epidemiological studies because the sensitivity is fairly low (less than 50 %), which may prevent the identification of cases of this rare disease.

Table 3
Validity and reliability of selected clinical instrumental variables and variable combinations.

Model	AUC	95 % CI	TP	TN	FP	FN	SE	SP	PPV	NPV	Correct	Cut-off probability
Step 1												
Feeding difficulties newborn period	0.68	0.62-0.74	70	94	31	55	56.0	75.2	69.3	63.1	65.6	0.68
Standing	0.53	0.48-0.57	23	109	16	102	18.4	87.2	59.0	51.7	52.8	0.54
Walking	0.55	0.51-0.60	26	112	13	99	20.8	89.6	66.7	53.1	55.2	0.48
Speech	0.54	0.47-0.60	69	65	60	56	55.2	52.0	53.5	53.7	53.6	0.52
Epilepsy	0.54	0.49-0.60	100	34	91	25	80.0	27.2	52.4	57.6	53.6	0.50
Infantile spasms	0.60	0.54-0.66	36	114	11	89	28.8	91.2	76.6	56.2	60.0	0.76
Focal seizures	0.58	0.51-0.64	69	75	50	56	55.2	60.0	58.0	57.3	57.6	0.56
Step 2												
Anteverted nares	0.53	0.50-0.56	11	121	4	114	8.8	96.8	73.3	51.5	52.8	0.68
Obesity	0.56	0.52-0.60	117	21	104	8	93.6	16.8	52.9	72.4	55.2	0.52
Hypotonia	0.61	0.55-0.68	93	59	66	32	74.4	47.2	58.5	64.8	60.8	0.54
Hypotonia present at visit	0.56	0.50-0.63	85	56	69	40	68.0	44.8	55.2	58.3	56.4	0.54
Developmental delay	0.50	0.44-0.57	–	–	–	–	–	–	–	–	–	–
Mental retardation	0.50	0.44-0.57	–	–	–	–	–	–	–	–	–	–
Step 3												
Spike-slow waves	0.52	0.45-0.58	–	–	–	–	–	–	–	–	–	–
Polyspike-slow waves	0.53	0.46-0.59	49	81	44	76	39.2	64.8	52.7	51.6	52.0	0.50
Combinations of variables												
Feeding difficulties newborn period + Hypotonia	0.71	0.65-0.78	53	111	14	72	42.4	88.8	79.1	60.7	65.6	0.64
Feeding difficulties newborn period + Hypotonia + Infantile spasms + Focal seizures	**0.75**	**0.70-0.81**	**62**	**111**	**14**	**63**	**49.6**	**88.8**	**81.6**	**63.8**	**69.2**	**0.62**

AUC: Area Under the ROC Curve; CI: confidence interval; TP: true positive; TN: true negative; SE: sensitivity; SP: specificity; VPP: positive predictive value; NPV: negative predictive value.

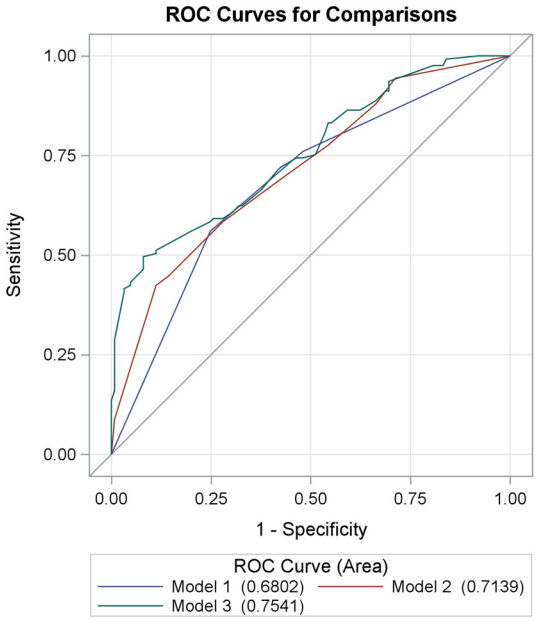

Fig. 1. Predictive value of models representing different combinations of signs, symptoms and instrumental findings.

Author contributions

EBe conceived the project and drafted the scientific report; GG coordinated the conduction of the study interacting with the local investigators; EBi did the statistical analyses; GR, VS, FA and RE interviewed and visited the patients; ME, PS, AV, NS and PB (the raters) examined the material from cases and controls.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.11.010.

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