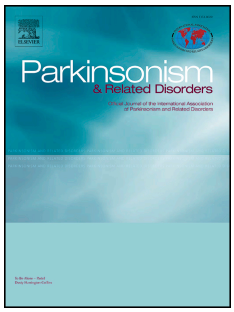
DOI:
10.1016/j.parkreldis.2016.10.001

Document Version
Peer reviewed version

Accepted Manuscript



Classification of dystonia in childhood

Daniel E. Lumsden, Hortensia Gimeno, Jean-Pierre Lin

PII: S1353-8020(16)30388-1

DOI: 10.1016/j.parkreldis.2016.10.001

Reference: PRD 3136

To appear in: *Parkinsonism and Related Disorders*

Received Date: 14 July 2016

Revised Date: 12 September 2016

Accepted Date: 3 October 2016

Please cite this article as: Lumsden DE, Gimeno H, Lin J-P, Classification of dystonia in childhood, *Parkinsonism and Related Disorders* (2016), doi: 10.1016/j.parkreldis.2016.10.001.

Classification of Dystonia in Childhood

Daniel E Lumsden*[1], Hortensia Gimeno[1,2] and Jean-Pierre Lin[1]

[1]Complex Motor Disorders Service, Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK
[2]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
*Corresponding Author:

daniel.lumsden@gstt.nhs.uk

Complex Motor Disorder Service, Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, Lambeth Palace Road, London SE1 7EH

Tel: +44 (0) 207 188 7188 Ext 8533
Fax: + 44 (0) 207 188 0851

Running Title: Classification Childhood Dystonia

Keywords: "Dystonia" "Childhood" "classification"

Financial Disclosures/Conflict of interest:

HG is currently funded by a National Institute for Health Research (NIHR/HEE Clinical Doctoral Research Fellowship, CDRF-2013-04-039 Clinical Academic Fellowship). This paper presents independent research funded by the NIHR. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health. DEL was supported by Dystonia Society UK grants 01/ 2011 and Action Medical

Research GN2097. J-PL has held grants from the Guy's and St Thomas Charity New Services and Innovation Grant G060708, the Dystonia Society UK Grants 01/2011 and 09/2013, and Action Medical Research GN2097. J-PL has acted as a consultant for Medtronic Ltd. The Complex Motor Disorders Service has benefited from unrestricted educational grants by Medtronic Ltd to present work at international conferences.

DEL, HG and JPL report no COI/FD directly relating to this study.

Word Count: 1918

Abstract

Objective:

The most recent international consensus update on dystonia classification proposed a system based on 2 axes, clinical characteristics and aetiology. We aimed to apply this system to Children and Young People (CAYP) selected for movement disorder surgery, and determine if meaningful groupings of cases could be extracted.

Methods:

The 2013 Consensus Committee classification system for dystonia was retrospectively applied to 145 CAYP with dystonic movement disorders. Two-step cluster analysis was applied to the resulting categorisations to identify groupings of CAYP with similar characteristics.

Results

Classification resulted in a total of 43 unique groupings of categorisation. Cluster analysis detected 4 main clusters of CAYP, comparable to previously used patient groupings.

Conclusions

The 2013 consensus update on dystonia classification can be applied to CAYP with dystonia. The large number of categories provides a wealth of information for the clinician, and also facilitates data driven grouping into clinically meaningful subgroups.

Introduction:

Dystonia is a common presentation in paediatric practice, differing from that seen in adult practice[1, 2], arising frequently as a symptomatic condition[3, 4], often found coincident with spasticity[1, 4] and with a motor phenotype expressed upon the back ground of ongoing brain development[2]. A number of definitions for dystonia have been proposed, most pertinently to paediatric practice being the definition of the Taskforce for Childhood Motor disorders, reported in 2003[5]. Almost 10 years after these definitions were proposed, a Consensus Committee established under the auspices of the Dystonia Medical Research Foundation, the Dystonia Coalition and the European Dystonia Cooperation and Technology published an updated definition for dystonia in 2013[6]. "*Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation*".

Accompanying this revised definition is a classification system along two axes 1) Clinical Characteristics and 2) Aetiology. A combination of the descriptors on the two set of axis was considered to *"provide meaningful information on any dystonia patient and serve as a basis for the development of research and treatment strategies".* This revised classification has potential benefits over those previously proposed, not least of which being the move away from the overly reductive division into "primary" and "secondary" dystonia, with the

attendant difficulties these terms have posed[6]. One potential benefit is also to facilitate syndromic associations, aiding recognition of distinct disease entities, ultimately aiding diagnosis.

We aimed to determine whether the proposed classification system could:

- Be applied to a consecutive cohort of children and young people (CAYP) undergoing Deep Brain Stimulation (DBS) surgery
- Provide meaningful grouping and subgroupings across this cohort from which to extract prognostic information

Following classification of 145 CAYP, a two-step cluster analysis was used to determine if clinically relevant sub-groupings could be identified across categorized subjects.

Methods:

From the Complex Motor Disorder Service Database, a cohort of CAYP were identified who had passed through the full assessment process for DBS surgery at our centre between July 2005 and January 2015 and had been considered suitable for surgery. The clinical notes of all CAYP identified were reviewed, and a standardized data pro-forma used to record data from each sub-category of the revised classification system. Classification was performed from data available at the point of baseline prior to potential surgery. Because the study was a retrospective audit of routine clinical

practice, ethics approval was not required and consent was neither required nor obtained.

Statistical analysis

Two-step cluster analysis was performed using SPSS Version 22 (IBM, Armonk, New York, USA). Categorical data for the sub-categories of the revised classification system was used to identify clusters of CAYP with similar dystonia characteristics. Clustering was achieved by a clustering feature tree, based on an agglomerative clustering algorithm. Selection of optimal clustering was achieved using Schwarz's Bayesian criterion. The quality of fit of the resultant modeled clusters was measured using the Silhouette measure of cohesion and separation. Data from “Body Distribution” and “Temporal Pattern – Variability” were excluded from analysis as almost all CAYP presented with generalized dystonia, and in all cases dystonia was persistent.

Results

Classification was possible for all 145 CAYP, resulting in 43 unique groupings of categories. The largest unique grouping consisted of 37 cases. These CAYP were classified as generalized dystonia with leg involvement, static course, persistent dystonic symptoms, combined dystonia, evidence of structural lesions on neuroimaging and acquired aetiology with onset < 2 years. Subjects within this group all met the diagnostic criteria for Cerebral Palsy. The next largest grouping consisted of 8 CAYP. A total of 20 unique groupings included just one CAYP.

2 step-cluster analysis suggested separation into 4 main clusters from these 43 unique groupings. The silhouette measure of cohesion and separation of 0.5 suggested a “fair” to “good” cluster segregation. The predominant characteristics of the clusters identified are outlined in Figure 1 and Table 1.

Discussion

For a cohort of CAYP with dystonic movement disorders selected for DBS surgery we have demonstrated: i) application of the most recently proposed dystonia classification system is possible, and ii) the system provides the means by which to generate clinically meaningful groupings in addition to providing richness of data at the individual level.

Classification systems for disease entities must necessarily evolve over time, as an understanding of underlying disease processes and prognostic factors for outcome grow. Dystonia classification has passed through numerous iterations following the initial groupings proposed by Fahn and Eldridge in 1976[7]. This original system introduced a system based on aetiology, with dystonia divided in “Primary”, “Secondary” or “Psychogenic”. Over time it has become recognized that the precise application of these classifications was troublesome, as outlined by Albanese and Colleagues in their Consensus Update[6].

The two-axis approach of the Consensus Update provides a clinical richness to the classification of dystonia previously lacking. Axis 1 and Axis 2 are sub-divided into 6 and 3 independent sub-categories respectively. Considering the sub-options within each of these categories (and leaving aside the listing of associated neurological features) >20000 possible independent sub-category combinations may be generated. In practice, not all of these groupings are clinically plausible (e.g. a perinatal brain injury giving rise to a paroxysmal dystonia in late adulthood). Reducing this vast range of options to a more practical number for the purposes of comparative work and prognostication is a necessity. Across a cohort of 145 CAYP we identified 43 independent unique classifications, reflective of the broad range of clinical syndromes giving rise to dystonia in childhood (only 64/145 CAYP presenting with isolated dystonia). From this large range of grouping, an independently driven cluster analysis was able to identified 4 subgroupings. In our previous reported we have pragmatically grouped CAYP with dystonia into categories of “Primary/Primary-plus”, “Secondary-Static” and “Secondary-Progressive”[8, 9]

Remarkably, these categorisations closely resemble the clusters resulting from our present analysis, Cluster 1 comparable to our Primary/Primary-Plus group, Cluster 2 our Secondary-Progressive (AKA heredo-degenerative) group and Clusters 3 and 4 resembling the Secondary-Static dystonia groupings (Cluster 3 due to CP, Cluster 4 due to other causes). Cluster analysis methods provide data driven techniques for identifying subjects across data sets with similar characteristics. Our present analysis provides some degree of validation both for our choice of these classifications in our

previous reports, and for the utility of the Consensus Update Classification itself. This validation is, however, limited by the population upon which the classification has been applied. As only cases within the paediatric age range have been included, caution must be taken in extrapolating our findings across more adult populations. Further validation of the Consensus Update Classification within the adult population is still required, as well as in a less highly specialist paediatric sampling.

Early onset-dystonias present specific challenges for classification. Children may present early in their disease course, prior to the evolution of all clinical/radiological features. Children with DYT1 dystonia will typically present with a focal dystonia, before generalization of dystonic symptoms over a variable time period, changing the pattern of anatomical classification. Similarly, for these children dystonic symptoms will appear to be progressive during the early stages of the disease course, before reaching a stable/static phase. Neuroimaging performed early in the disease course for neurodegenerative disorders (e.g. Neuronal degeneration with brain iron accumulation) may not yet demonstrate characteristic abnormalities. Categorisation of individual CAYP may change over time, and should be considered a dynamic process rather then a static label. Our presented study has not examined the stability of classification over time, and further work is required to explore how frequently the classification of a given child should be revisited, potentially an important consideration for studies of the natural history of this patient population.

One limitation of the Consensus classification system is the lack of information regarding functional status of subjects. We believe that this information is imperative when evaluating interventions such as DBS. We have recently demonstrated the relationship between a number of functional scales commonly used in children with CP and the Burke-Fahn-Marsden-Dystonia rating scale across a heterogenous cohort of children with hyperkinetic movement disorders[10]. These scales provide interrelated but complementary information and we would encourage their adoption when reporting the evaluation of subjects with dystonia.

It has been argued that primary dystonia remains a valuable clinico-etiological construct to guide clinical decision making with respect to diagnostic testing and management options[11]. Of particularly interest for our presented cohort is how classification could guide expectations regarding outcome following DBS. Prognostic factors for outcome following pallidal DBS remain largely unclear, though one clear finding is that, taken collectively, dystonia previously categorised as “secondary” is less responsive than dystonia previously catergorised as primary[12]. However, even this apparently clear cut relationship has it’s exceptions (e.g. the apparent responsiveness of tardive dyskinesia to DBS). Whilst generally positive results are expected, even within the genetically defined primary dystonias a range of responsiveness may be seen. We agree that a dichotomous classification into either primary or secondary dystonia is overly reductive. More nuanced delineation is required as to sub-groups across these populations, as well as variables running continuously across the group (e.g. duration of dystonia and

proportion of life lived with dystonia). What factors linking these groups along a continuum may be just as important for prognosis as categorical variables separating groupings.

As noted above, the major limitation of the presented study is the nature of the population from which it is drawn. Whilst we believe the children and young people to whom we have applied the classification system are representative of those presenting to other services for consideration for DBS surgery, they are not fully representative of the range of presenting more generally to health services with dystonic movement disorders. There is likely to be both under and over representation of specific patient sub-groups. The most important consequence of this may be the introduction of an inadvertent bias in the clusters identified by the subsequent statistical analysis. These clusters may, whilst representing common groupings of CAYP undergoing assessment for Deep Brain Stimulation, not prove replicable in studies drawing from a less highly specialist clinical or academic sampling of childhood dystonia. It is likely that additional clusters could be identified in a broader sampling. It remains to be seen whether the clusters we have identified would continue to emerge from a larger sampling, or would these CAYP be subsumed into other groupings entirely.

The body distribution of dystonia and the variability of temporal pattern were not included in the cluster analysis given they were almost invariant across the CAYP sampled. In a larger, less selective cohort, these factors are likely to have become more important. Similarly, invariably with the inclusion of a

broader age range of adults with dystonia, clusters with later onset dystonia must be anticipated. It would be expected that in a large, representative sample across a broad age range of subjects with dystonia one cluster likely to emerge would be an adult onset focal/segmental dystonias corresponding to patients with cervical dystonia.

In conclusion, the 2013 consensus update on dystonia classification can be applied to CAYP with dystonia, providing a wealth of information for the clinician, and facilitating data driven grouping into clinically meaningful subgroups. We encourage other groups caring for children and/or adults with dystonia to perform similar data driven analysis to determine whether the groupings we have identified represent consistent categories across childhood dystonia, or are unique to our cohort, and also what further groupings can be identified across the adult age range.

Author Contributions

DEL: Research Project Conception, Design, Execution,

Statistical Analysis

Manuscript: Preparation of first and subsequent drafts

HG: Research Project Conception, Design, Execution

Manuscript – review and critique

JPL: Manuscript: Review and critique

[1] Roubertie A, Mariani LL, Fernandez-Alvarez E, Doummar D, Roze E. Treatment for dystonia in childhood. Eur J Neurol. 2012;19:1292-1299
[2] Mink JW. Special concerns in defining, studying, and treating dystonia in children. Mov Disord. 2013;28:921-925.

[3] Roubertie A, Rivier F, Humbertclaude V, Tuffery S, Cavalier L, Cheminal R, Coubes P, Echenne B. [The varied etiologies of childhood-onset dystonia]. Rev Neurol (Paris). 2002;158:413-424.
[4] Lin JP, Lumsden DE, Gimeno H, Kaminska M. The impact and prognosis for dystonia in childhood including dystonic cerebral palsy: a clinical and demographic tertiary cohort study. J Neurol Neurosurg Psychiatry. 2014;85:1239-1244.
[5] Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. Pediatrics. 2003;111:e89-97.
[6] Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallet M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: A consensus update. Mov Disord. 2013;28:863-73.
[7] Fahn S, Eldridge R. Definition of dystonia and classification of the dystonic states. Adv Neurol. 1976;14:1-5.
[8] Gimeno H, Tustin K, Lumsden D, Ashkan K, Selway R, Lin JP. Evaluation of functional goal outcomes using the Canadian Occupational Performance Measure (COPM) following Deep Brain Stimulation (DBS) in childhood dystonia. Eur J Paediatr Neurol. 2014;18:308-316.
[9] Lumsden DE, Kaminska M, Gimeno H, Tustin K, Baker L, Perides S, et al. Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. Dev Med Child Neurol. 2013;55:567-574.
[10] Elze MC, Gimeno H, Tustin K, Baker L, Lumsden DE, Hutton JL, Lin JP. Burke-Fahn-Marsden dystonia severity, Gross Motor, Manual Ability, and Communication Function Classification scales in childhood hyperkinetic movement disorders including cerebral palsy: a 'Rosetta Stone' study. Dev Med Child Neurol. 2016;58:145-153.
[11] Bressman SB, Saunders-Pullman R. Primary dystonia: moribund or viable. Mov Disord. 2013;28:906-913.
[12] Andrews C, Aviles-Olmos I, Hariz M, Foltynie T. Which patients with dystonia benefit from deep brain stimulation? A metaregression of individual patient outcomes. J Neurol Neurosurg Psychiatry. 2010;81:1383-1389.

Figure Legends:

Figure 1:

Results of cluster analysis across 145 CAYP with dystonia. Running from top to bottom rows demonstrated – Percentage of cohort in each Cluster

(absolute number of subject), Nervous System Pathology (bars from left to right – Evidence of degeneration, evidence of structural lesion and no evidence of degeneration or structural lesion), Temporal Pattern (bars from left to right – static and progressive), Cause of dystonia (bars from left to right - autosomal recessive, Perinatal brain injury, idiopathic-sporadic, Idiopathic-familial, Vascular, Mitochondrial, infection, x-linked and Autosomal domninant), Isolated or Combined (bars from left to right – Isolated and combined), and Age of Onset (bars from left to right - <2 years, 3-12 years, 13-20 years). Rows are ordered from top to bottom in descending order of importance to the model prediction.

Cluster Number	Cluster Size (n)	Characteristics of Cluster
1	48	Predominantly no evidence of degeneration or structural lesion, static disease course, mixed autosomal dominant/x-linked/idiopathic-familial inheritance, predominantly combined dystonia, mixed age of onset
2	38	Predominantly evidence of degeneration, progressive dystonia course, mixed autosomal recessive/x-linked inheritance, isolated dystonia and onset <12 years
3	38	Predominantly evidence of structural lesion, static dystonia course, acquired perinatal brain injury, combined dystonia, and onset <2 year
4	23	Predominantly evidence of structural lesion, static dystonia course, mixed acquired infection/vascular, isolated dystonia, onset >12 years

Table 1: Characteristics of Cluster identified by cluster analysis process

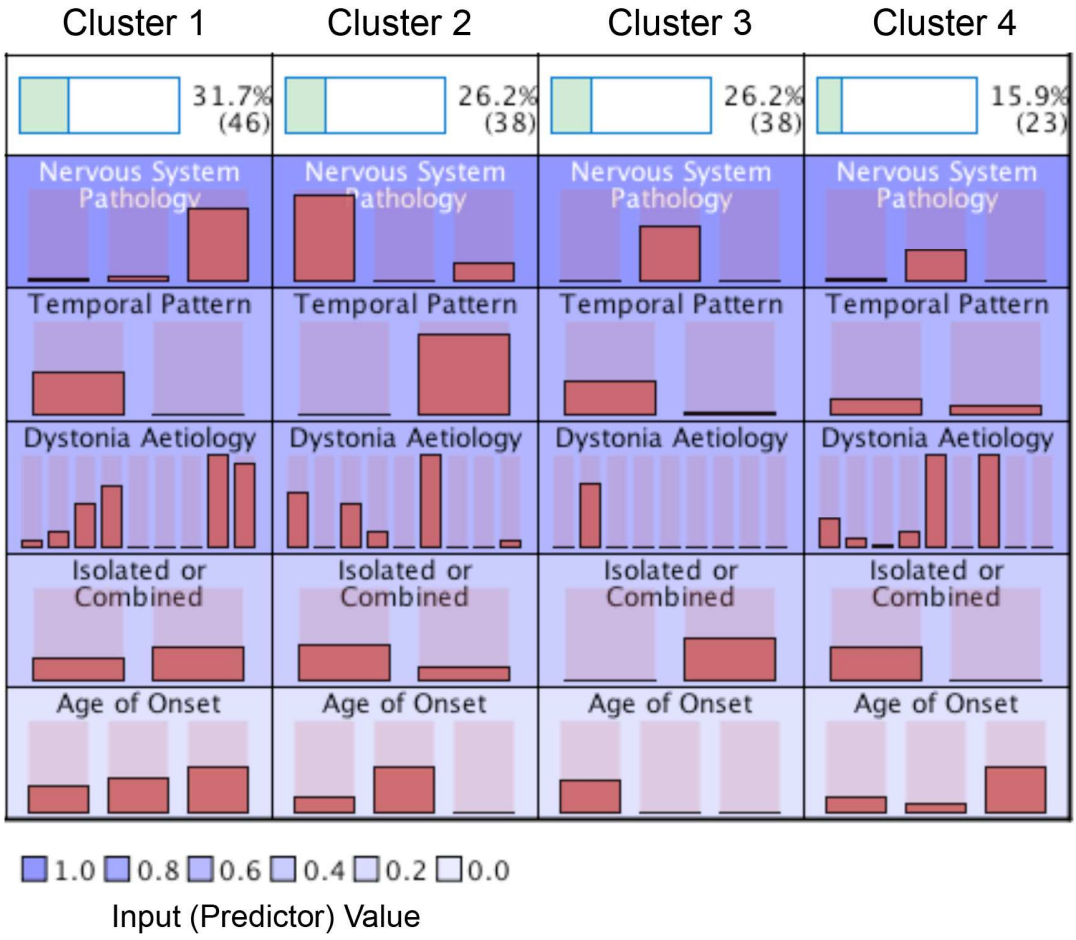


Figure 1

Highlights

- Dystonia in childhood is a highly heterogenous condition
- The 2013 Consensus Classification system can be applied to children and young people
- Classification of 145 children resulted in 43 unique categorical groupings
- Cluster analysis following classification identified 4 major biological plausible subgroupings.