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Speech Disturbances in Patients With Dystonia or Chorea Due to Neurometabolic Disorders

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Abstract: Speech disturbances are frequent and potentially disabling in patients with dystonia or chorea due to neurometabolic disorders (DCND), but their precise characteristics are poorly documented. We prospectively studied 29 consecutive patients with DCND. A detailed description of their speech patterns was obtained by using the Frenchay dysarthria assessment test and the apraxia of speech evaluation test of Wertz. Gross motor function and intelligibility were each scored on 5-point scales to identify a possible correlation between the severity of the speech and motor disorders. All the patients were found to have complex speech alterations with combined features of hyperkinetic dysarthria and speech apraxia. We also noted a correlation between the severity of the speech disorders and the motor disorders. These findings have important implications for speech rehabilitation, and may provide new insights into the pathophysiology of dystonia due to neurometabolic disorders. © 2010 Movement Disorder Society

Key words: speech apraxia; hyperkinetic dysarthria; dystonia; glutaric aciduria type 1; Lesch-Nyhan disease; GM1 gangliosidosis type 3

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Speech disturbances are frequent and potentially disabling in patients with dystonia or chorea due to neurometabolic disorders (DCND), particularly glutaric aciduria type 1 (GA1), Lesch-Nyhan disease (LND), and GM1 gangliosidosis type 3 (GM1g3).[1–3] They are often an early manifestation, and remain a prominent feature throughout the disease course. In two large series of GA1 patients, dysarthria was present in 64% of

77 cases and 85% of 28 cases.[4,5] Dysarthria was also present in all but 1 patient in the largest review of GM1g3 patients (n = 48),[1] and in all 44 patients included in the largest consecutive series of LND patients.[3]

The clinical phenomenology of speech disorders in this setting is poorly documented, and there are no specific guidelines for speech rehabilitation. The aim of this study was to provide a detailed description of speech disturbances in consecutive patients with DCND, and to propose appropriate approaches for speech rehabilitation. We also examined whether the severity of the speech disturbances is related to motor status.

PATIENTS AND METHODS

Patients

We prospectively enrolled consecutive symptomatic patients with firm diagnoses of DCND who attended the neurology department of Bicêtre hospital for speech evaluation, over a 1-year period. The inclusion criteria were the following: (1) a neurometabolic disorder documented by appropriate biochemical and/or genetic studies, (2) dystonia or chorea related to the neurometabolic disorder, (3) age over 3 years, (4) French mother tongue, and (5) cognitive status compatible with comprehension of instructions required for speech evaluation.

Study Design

The patients had a standardized interview (with the help of their family when necessary) and neurological examination. The Gross Motor Function Classification System (GMFCS, score range 0 to 5) was used to assess motor capacity.[6] The patients also had a comprehensive standardized speech examination conducted by the same trained speech therapist (C.F.-R.), focusing on the phenomenology of their speech disorders. Finally, a short non verbal neuropsychological test was administered, taking into account motor and speech disabilities and fatigability, using the Raven Progressive Matrices (PM38 or PM47, depending on age).[7]

Speech Examination

Dysarthria was evaluated clinically, using a French adaptation of the Frenchay Dysarthria Assessment developed by Enderby.[8,9] Part of this evaluation (25 items) assesses reflex activities such as swallowing and respiration, and the motricity of the larynx, lips, tongue, jaw, and velum in tasks with and without speech. Each item was scored on a 9-point scale (0–8: 8 corresponding to normal performance). The other part of this evaluation focuses on intelligibility (see later).

In addition, the patients were tested for speech apraxia by using a French adaptation of the apraxia of speech evaluation test of Wertz,[10,11] which consists of 11 items. The six first items assess repetition of phonemes and syllables, words, logatomes and sentences, and repeated production of the same utterance. The last five items assess speech alteration during singing, conversational situations and reading (if possible), and discrepancies in speech accuracy between automatic-reactive and volitional-purposive speech.

Intelligibility was evaluated during conversational speech and while reading words and sentences. When the patients were unable to read, intelligibility was tested during oral description of a complex picture. An in-house intelligibility scale with six possible scores (0 to 5) was used to measure speech capacity and likely repercussions in daily life, as follows: (0) no speech deficiency for age; (1) rare phonemic transformations and/or articulatory deficits not affecting intelligibility; (2) frequent phonemic transformations and/or articulatory deficits requiring particular attention by the person the patient is speaking to; (3) permanent phonemic transformations and/or articulatory deficits that markedly disturb speech as a whole, requiring frequent repetition of the item by the patient, some sentences being unintelligible; (4) speech totally unintelligible for persons unacquainted to the patient; and (5) no speech.

Statistical Analysis

We used the Spearman rank correlation coefficient to examine relationships between the severity of speech disorders (measured with the in-house intelligibility scale) and the severity of motor dysfunction (GMFCS). All 29 patients were included in the analysis, and there were no missing data. The threshold of significance was set at $P < 0.05$. StatView statistical software was used for all analyses.

RESULTS

A total of 29 patients from 27 families were enrolled in the study. General characteristics of the patients are shown in Table 1. All the patients had a firm diagnosis of neurometabolic disease, based on biochemical and/or genetic studies. Eleven patients had LND, 11 had glutaric aciduria type 1, four had GM1 gangliosidosis type 3, two had methylmalonic aciduria, and one had

TABLE 1. *Main characteristics of the patients*

Patient	Diagnosis	Biochemistry/molecular analysis	Age at onset/at examination	Main MDS	Other neurological abnormalities	Cognitive level	GMFCS	Intelligibility score
1	GA1	Elevated glutaric acid in urine *GCDH* gene: NA	4 mo/6 yr	Dystonia	Chorea Axial hypotonia	90	3	2
2	GA1	Elevated glutaric acid in urine *GCDH* gene: NA	17 mo/16 yr	Dystonia	Pyramidal syndrome	105	1	2
3	GA1	Elevated glutaric acid in urine *GCDH* gene: NA	10 mo/13 yr	Dystonia	Chorea Axial hypotonia	60	4	4
4	GA1	GCDH activity: 2% *GCDH* gene: R402W + R227P	10 mo/20 yr	Myoclonic dystonia	Chorea Parkinsonism Axial hypotonia	105	1	1
5	GA1	GCDH activity: 11% *GCDH* gene: R227P+A293T	4 mo/6 yr	Dystonia	Chorea Axial hypotonia	100	4	2
6	GA1	*GCDH* gene: R227P + A293T	18 mo/8 yr	Chorea	Dystonia Axial hypotonia	100	1	1
7	GA1	Elevated glutaric acid in urine *GCDH* gene: NA	4 mo/9 yr	Dystonia	Chorea Axial hypotonia Pyramidal syndrome	NA	5	4
8	GA1	GCDH activity: 2% *GCDH* gene: NA	8 mo/13yr	Chorea	Dystonia Axial hypotonia	100	1	1
9	GA1	Elevated glutaric acid in urine N392X + c1173_1174insT	birth/24 yr	Dystonia	Chorea Athetosis Pyramidal syndrome Seizures	90	2	2
10	GA1	Elevated glutaric acid in urine *GCDH* gene: NA	9 mo/26 yr	Dystonia	Chorea Axial hypotonia Parkinsonism Pyramidal syndrome Seizures	NA	4	5
11	GA1	Elevated glutaric acid in urine *GCDH* gene: R402W + R402W	birth/28 yr	Dystonia	Parkinsonism Axial hypotonia Seizures	110	5	5
12	LND	HPRT activity: 0 *HPRT1* gene: H39D	6 mo/15 yr	Dystonia	Chorea Axial hypotonia Pyramidal syndrome Self injury	90	4	2
13	LND	HPRT activity: 0 *HPRT1* gene: F99fsX8	9 mo/4 yr	Dystonia	Athetosis Parkinsonism Axial hypotonia Pyramidal syndrome Self injury	NA	4	4
14	LND	HPRT activity: 0 *HPRT1* gene:S162fsX4	1 mo/6 yr	Dystonia	Axial hypotonia	NA	5	2
15	LND	HPRT activity: 0 *HPRT1* gene: Q152X	6 mo/27 yr	Dystonia	Axial hypotonia Seizures Self injury	NA	5	2
16	LND	HPRT activity: 0.13 *HPRT1* gene: G16V	6 mo/22 yr	Dystonia	Axial hypotonia Pyramidal syndrome Self injury	NA	5	3

(Continued)

TABLE 1. *(Continued)*

Patient	Diagnosis	Biochemistry/molecular analysis	Age at onset/at examination	Main MDS	Other neurological abnormalities	Cognitive level	GMFCS	Intelligibility score
17	LND	HPRT activity: 0 *HPRT1* gene: D44H	4 mo/13 yr	Dystonia	Axial hypotonia Self injury	NA	5	2
18	LND	HPRT activity: 0 *HPRT1* gene: D80F	6 mo/16 yr	Dystonia	Axial hypotonia Pyramidal syndrome	80	3	2
19	LND	HPRT activity: 0.09% *HPRT1* gene: 28delY	4 mo/16 yr	Dystonia	Axial hypotonia Pyramidal syndrome Self injury	NA	5	4
20	LND	HPRT activity: 0 *HPRT1* gene: G40R	4 mo/18 yr	Dystonia	Chorea Axial hypotonia Self injury	NA	5	4
21	LND	HPRT activity: 8% *HPRT1* gene: F199C	3 yr/43 yr	Dystonia	Pyramidal syndrome	100	1	1
22	LND	HPRT activity: 0 *HPRT1* gene: Y28STOP	5 mo/3 yr	Dystonia	Axial hypotonia	NA	5	2
23	GM1g	GLB activity: 8.7% *GLB1* gene: G438E + G438E	3 yr/19 yr	Dystonia	Parkinsonism	NA	5	5
24	GM1g	GLB activity: 2.7% *GLB1* gene: G438E+G438E	7 yr/23 yr	Dystonia	Parkinsonism Myoclonus	NA	4	5
25	GM1g	GLB activity: 6% *GLB1* gene: NA	2 yr/37 yr	Dystonia	Parkinsonism Pyramidal syndrome	90	4	5
26	GM1g	GLB activity: 5% *GLB1* gene: R148C+ K73E	16 yr 28 yr	Dystonia	Parkinsonism	115	4	3
27	MMA	MCM activity: mut (–) *MUT* gene:N219Y + Q383H	3 yr/13 yr	Dystonia	Chorea Tremor	100	1	2
28	MMA	MCM activity: mut (–) *MUT* gene: R474X+R511X	17 mo/11 yr	Chorea	Dystonia Axial hypotonia	80	1	2
29	L-2OH-GA	Elevated L-2-hydroxyglutaric acid in urine Large homozygous deletion (exon1 to 10) In the *L2HGDH* gene	9 mo/13yr	Tremor	Dystonia	50	3	2

yr, years; mo, months; NA, not available; GA1, glutaric aciduria type 1; LND, Lesch-Nyhan disease; GM1g, gangliosidis GM1 type 3; MMA, methylmalonyl aciduria; L-2OH-GA, L-2 hydroxy glutaric aciduria; GCDH, Glutaryl coA deshydrogenase; HPRT, Hypoxanthine-guanine phosphoribosyltransferase; GLB, beta-galactosidase; MCM, Methylmalonyl CoA Mutase; GMFCS, Gross Motor Function Classification System.

L-hydroxyglutaric aciduria. Seventeen patients were male (all the patients with LND were male, as the disease is X-linked). Median age was 16 years (range 3–43 years). Dystonia was present in all 29 patients; it was generalized and represented the predominant movement disorder in 25 cases.

Detailed results of the standardized speech examination are shown in Figure 1. The speech disorder was mild in 4 patients (score 1 on the intelligibility scale), moderate in 14 (score 2), and severe in 11 (score 3, 4, or 5). All the patients had complex alterations of speech, consistent with combined hyperkinetic dysarthria (aprosodia, imprecise articulation, slow rate of speech, short breathes of speech, and vocal forcing) and speech apraxia (effortful groping for articulatory gestures, difficulties with the initiation of utterances, and context-dependent variability of speech performance). The nature of the speech disorders was similar in LND and GA1 patients, but they tended to be more severe in LND.

In addition to speech disorders, 18/29 patients (LND = 7/11, AG1 = 5/11, GM1 = 4/4, AMM = 1/2, L2OH = 1/1) had swallowing difficulties.

Seventeen patients were able to complete the Raven progressive matrices test. Their median score was 100 (range 50–115) and 15/17 patients had scores within the normal range (>80). The remaining 12 patients were unable to complete the test, owing to very severe speech and motor disorders or to fatigability.

Intelligibility deteriorated as the severity of motor dysfunction increased ($\rho = 0.55$; $z = 2.66$; $P < 0.01$) (Fig. 2).

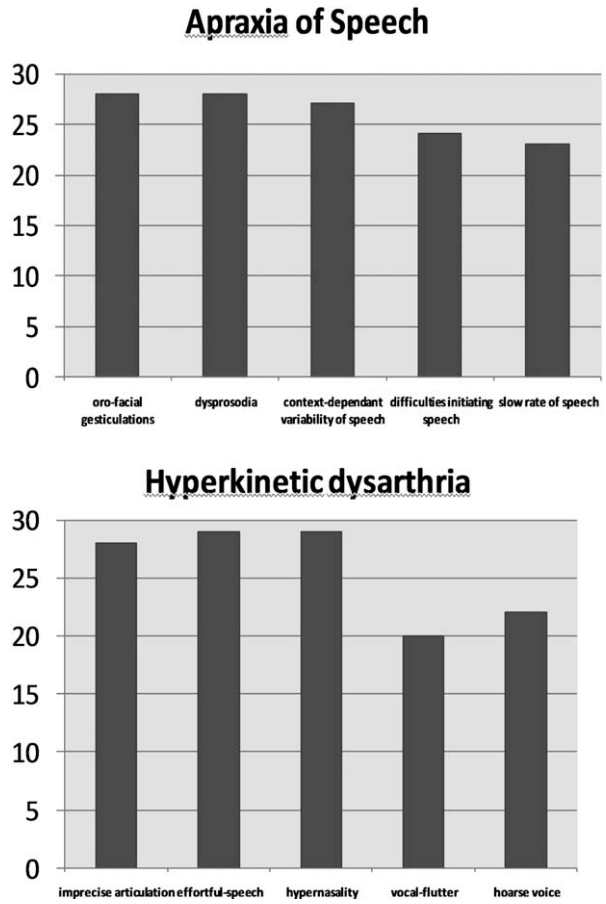

FIG. 1. Detailed results of speech examination, showing the association between speech apraxia (top) and hyperkinetic dysarthria (bottom) in DCND patients.

DISCUSSION

In this study of 29 consecutive patients with DCND, we observed uniform and complex speech alterations with combined features of hyperkinetic dysarthria and speech apraxia. This particular combination typically manifested as slow, dysprosodic and effortful speech, with imprecise articulation and hypernasality. Speech-induced orofacial gesticulations and insufficient respiratory support for speech were consistently observed. We also found a positive correlation between the severity of the speech disorders and the motor disorders. These findings have important implications for speech rehabilitation, and may provide new insights into the pathophysiology of dystonia due to neurometabolic disorders.

One possible limitation of this study is that we cannot ascertain that the speech alterations were not due to mental retardation in the 2 patients with low IQ (<80) or the 12 patients who did not complete the cognitive tests. However, two observations argue against a link between mental retardation and speech alterations in DCND: (i) The pattern of speech alteration was similar in patients with and without mental retardation in this study; (ii) The original speech pattern observed here, combining hyperkinetic dysarthria and speech apraxia, has not previously been reported in mentally retarded patients.

Hyperkinetic dysarthria is the prototype speech disorder in patients with various forms of dystonia, and

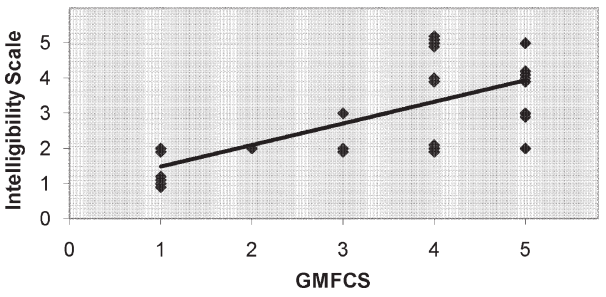

FIG. 2. Positive correlation between the severity of motor disorders (GMFCS) and the severity of speech disorders (intelligibility score); $\rho = 0.55$, $z = 2.66$, $P < 0.01$.

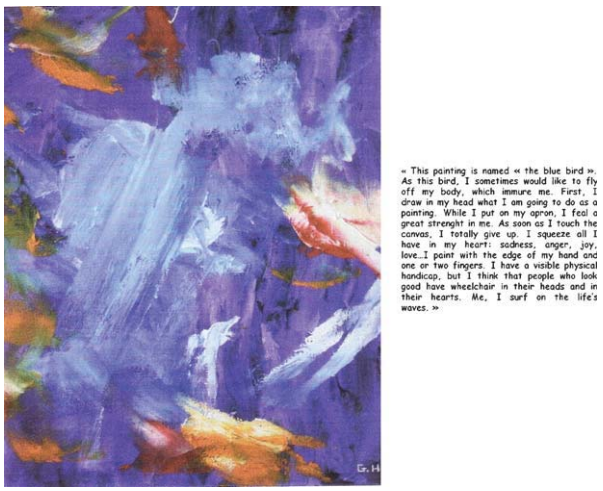

FIG. 3. This painting by a GA1 patient with major speech disorders illustrates the possibility of developing alternative means of communication and artistic skills.

particularly primary generalized dystonia, which is occasionally associated with speech impairment.[12] Most DCND patients in this study had secondary generalized dystonia and not only hyperkinetic dysarthria but also speech apraxia, i.e. an impaired capacity to plan or program commands that direct speech movements.[13,14] This may reflect the fact that DCND patients have more diffuse neuronal dysfunction than patients with primary dystonia, with involvement of the pathways involved in speech programming. This combination of movement disorders and speech apraxia has been described in neurodegenerative disorders such as cortico-basal degeneration and supranuclear palsy.[15]

Our findings point to certain approaches that might improve speech rehabilitation in this setting.[16–18] This is important for clinical practice, as communication difficulties have a major impact on these patients' daily lives. Based on the phenomenology of the speech disorders observed here, speech therapy should include (i) breathing exercises with and without oralisation, to improve coordination between respiration and phonation and, thus, speech initiation and verbal output; (ii) traditional articulatory kinematic rehabilitation; (iii) exercises to strengthen the soft palate and diminish hypernasality; (iv) work on rhythm modifications, using pacing to improve dysprosody and speech fluidity; (v) intersystemic facilitation/reorganization approaches based on singing and melody therapy to improve dysprosody and speech programming. These specific approaches should be combined with more classical approaches, including (i) auditory feed-back to improve intelligibility; (ii) encouragement to communicate actively with family and friends; and (iii) early use of alternative forms of communication, particularly in patients with severe speech disorders (Fig. 3).

Childhood onset of speech disorders is the rule in DCND. This is likely to undermine language learning and could result in psycholinguistic inhibition in adulthood. Speech rehabilitation should therefore start as early as possible. In patients with an early brain insult, like those studied here, the expected gain from rehabilitation depends on the type and severity of the damage, and on the balance between the high plasticity and high vulnerability of the immature brain.[19–23] Despite increased brain plasticity,[19,20] children with earlier brain insult of various origins are likely to have poorer recovery than those with later insult.[21–23] This may be due to damage, at a critical stage of development, to brain regions essential for the subsequent development (or restoral) of specific skills.[21]

The original and consistent speech pattern observed here in patients with DCND may be related more to the location and age at onset of early neurological lesions than to the underlying metabolic defect. Indeed, most forms of DCND are characterized by predominant striatal involvement and onset in the first years of life.[1–3,24] The striatum and the basal ganglia network are probably important to generate components of speech motor programs (particularly those that help to maintain a stable musculoskeletal environment in which discrete speech movements can occur) and for implementation of speech motor planning routines.[25–27] It should, however, be noted that the correlation observed here between the severity of the motor and speech disorders was based on the use of a in-house rating scale of intelligibility that has not been externally validated.

In Parkinson's disease, another disorder involving basal ganglia dysfunction and both motor and speech disorders, motor symptoms are markedly dopa-responsive, while laryngeal and articulatory speech components are not under predominent dopaminergic control.[28–30] There is therefore no correlation between speech intelligibility and disease severity,[31] and the progression of dysprosody does not correlate with motor deterioration.[32] Our findings suggest that the motor and speech disorders associated with DCND result, at least in part, from common pathophysiological mechanisms and/or common structural damage. In DCND, speech and motor disorders may represent two facets of the same process, dystonia corresponding to altered motor programming[33–35] and speech apraxia to altered speech programming.[13,14]

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