Phenotypic Variability in Developmental Coordination Disorder: Clustering of Generalized Joint Hypermobility With Attention Deficit/hyperactivity Disorder, Atypical Swallowing and Narrative Difficulties

CLAUDIA CELLETTI, GIORGIA MARI, GIULIA GHIBELLINI, MAURO CELLI, MARCO CASTORI, AND FILIPPO CAMEROTA

Developmental coordination disorder (DCD) is a recognized childhood disorder mostly characterized by motor coordination difficulties. Joint hypermobility syndrome, alternatively termed Ehlers–Danlos syndrome, hypermobility type (JHS/EDS-HT), is a hereditary connective tissue disorder mainly featuring generalized joint hypermobility (gJHM), musculoskeletal pain, and minor skin features. Although these two conditions seem apparently unrelated, recent evidence highlights a high rate of motor and coordination findings in children with gJHM or JHS/EDS-HT. Here, we investigated the prevalence of gJHM in 41 Italian children with DCD in order to check for the existence of recognizable phenotypic subgroups of DCD in relation to the presence/absence of gJHM. All patients were screened for Beighton score and a set of neuropsychological tests for motor competences (Movement Assessment Battery for Children and Visual-Motor Integration tests), and language and learning difficulties (Linguistic Comprehension Test, Peabody Picture Vocabulary Test, Boston Naming Test, Bus Story Test, and Memoria-Training tests). All patients were also screening for selected JHS/EDS-HT-associated features and swallowing problems. Nineteen (46%) children showed gJHM and 22 (54%) did not. Children with DCD and gJHM showed a significant excess of frequent falls (95 vs. 18%), easy bruising (74 vs. 0%), motor impersistence (89 vs. 23%), sore hands for writing (53 vs. 9%), attention deficit/hyperactivity disorder (89 vs. 36%), constipation (53 vs. 0%), arthralgias/myalgias (58 vs. 4%), narrative difficulties (74 vs. 32%), and atypical swallowing (74 vs. 18%). This study confirms the non-causal association between DCD and gJHM, which, in turn, seems to increase the risk for non-random additional features. The excess of language, learning, and swallowing difficulties in patients with DCD and gJHM suggests a wider effect of lax tissues in the development of the nervous system.

KEY WORDS: attention deficit/hyperactivity disorder; coordination; language; hypermobility; speech; swallowing


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INTRODUCTION

The term “development coordination disorder” (DCD) is used to define the selective impairment of development of motor coordination in children [Vaire-Douret, 2014]. Synonyms of DCD include, but are not limited to congenital clumsiness, “motor debility” and developmental dyspraxia, the latter being the result of faulty maturational processes of the central nervous system during infancy and childhood [Vaire-Douret, 2014]. According to the diagnostic and statistical manual of mental disorders (DSM-IV) [American Psychiatric Association, 2000], DCD is an exclusion diagnosis for perturbed fine and/or global motor coordination in the absence of any cognitive, neurological, and/or sensorial deficit. The overall prevalence of DCD is close to 6% in children with an excess of affected males [American Psychiatric Association, 2000]. Motor impairments include marked delay in achieving motor milestones, clumsiness, poor sensorimotor coordination, poor balance and handwriting and poor postural control, as well as difficulties in motor learning (acquiring and automating new movements), execution and ideation of motor planning, timing, and sequencing of movement [Geuze, 2005]. Thus far, the etiology of DCD remains unknown, despite many hypotheses that have been suggested to explain its neurodevelopmental pathogenesis.

Kirby and Davies [2007] observed functional similarities between children with DCD and those with joint hypermobility syndrome (JHS), a connective tissue disorder diagnosed according to the Brighton criteria [Grahame et al., 2000]. This observation prompted the authors to speculate on the multisystem nature of DCD. JHS, which is now considered clinically indistinguishable from Ehlers–Danlos syndrome, hypermobility type (JHS/EDS-HT) [Tinkle et al., 2009; Castori et al., 2014], presents manifestations that span clearly beyond the integumentary and articular systems [Castori, 2012]. The proposed link between connective tissue and DCD is also supported by the observation of a high prevalence of generalized joint hypermobility (gHM) in children with DCD [Jelsma et al., 2013]. These data corroborate what has been previously observed by Adib et al. [2005], who described clumsiness and poor coordination symptoms in 125 children with JHS. They also described speech and learning difficulties, as well as “dyspraxia” among these patients.

It is possible that the lack of recognition of a significant overlap between DCD, gHM, and JHS/EDS-HT is due to the still widespread lack of prompt diagnosis of gHM and related syndromes in specialized settings (i.e., among rheumatologists) [Grahame and Bird, 2001]. This is probably related to the absence of a consensus among specialists in using available diagnostic criteria for gHM and JHS/EDS-HT [Remvig et al., 2014], as well as the absence of a reliable confirmatory test for JHS/EDS-HT [Mayer et al., 2013]. Hence, the non-random association between DCD, gHM, and associated symptoms may represent a highly prevalent, still poorly defined, multisystem disorder in children, with unexpected consequences on various health and mental health determinants in adults.

In the short term, the early recognition of gHM and related features may be useful for the assessment and management of the child with DCD under both the clinical and the rehabilitation perspectives. The aim of the present study is to assess the prevalence of gHM in a group of 41 Italian children with DCD and to investigate possible phenotypic clustering in relation to additional findings, such as language disorders and learning impairments.

MATERIALS AND METHODS

From May 2012 to February 2013, 41 Italian children with DCD were assessed in a specialized setting including child neurologist, logopedist and physiatrist. The diagnosis of DCD was made according to DSM-IV [American Psychiatric Association, 2000]. Exclusion criteria were age <4 years, IQ <70 evaluated through the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV) [Wechsler, 2003], as well as the presence of any neurological, rheumatic, and metabolic disease.

Motor performance was evaluated using the Movement Assessment Battery for Children (M-ABC) test [Henderson and Sugden, 1992] and the Developmental Test of Visual–Motor Integration (VMI) test [Sutton et al., 2011]:

- M-ABC is a product-oriented, norm-referenced test designed for (a) identifying children aged 4–12 years with motor difficulties; (b) clinical exploration, intervention planning; (c) program evaluation; and (d) research. It consists of eight items grouped in three sections (manual dexterity, ball skills, and balance).
- VMI is commonly used to assess handwriting dysfunction in children. VMI is a standardized, norm-referenced test designed to assess visual–motor integration. VMI requires the child to copy a series of geometric designs. Child's performance is compared with standard criteria and reference designs and a score allocated according to the accuracy of the drawing.

All the children were first evaluated for gHM, language disorders, and learning disabilities. gHM was assessed with the Brighton score [Beighton et al., 1973] by two trained physiatrists. This score is composed of five maneuvers: four of them are tested passively on both sides of the body and one is tested actively. The passive extension of the metacarpophalangeal joint of the little finger, elbow, and knee were measured bilaterally. When the range of motion exceeds a specified range, 1 point is given. These points are summed and the score ranges from 0 to 9 (two times four joints and 1 point for hands flat on the floor with straight knees). According to the recommendation of van der Giessen, the cut-off point for hypermobility was ≥5 for children aged 3–9 years and ≥4 points for children aged older than 10 years [van der Giessen et al., 2001].

Language and learning difficulties were assessed using the Linguistic Comprehension Test (LCT) [Rustioni, 1994], The Peabody Picture Vocabulary Test (PPVT) [Dunn and Dunn, 1981], the Boston Naming Test (BNT) [Kaplan et al., 2014], and the Stanford Achievement Test (SAT) [Stanford Achievement Test, 1993].
et al., 1976] the Bus Story Test (BST) [Renfrew, 1969], and the Memory-Training (MT) Test for the Assessment of reading and comprehension skills [Cornoldi and Colpo, 1998]:

- LCT is an Italian-specific and Italian-normed test of linguistic understanding; it is packaged in booklet form in a multiple-choice format, and is used to assess the understanding of grammatical contrasts in the Italian language. The child is shown a page with four picture choices and must select the picture that matches a spoken sentence. The test is administered in six different protocols depending on age, and the score is calculated as the sum of correct answers.

- PPVT measures an individual's receptive vocabulary for standard American English and provides, at the same time, a quick estimate of verbal ability or academic aptitude. It has been translated in Italian language [Stella et al., 2000]. The PPVT consists of 175 stimulus words and as many corresponding image plates. Each image plate contains four black-and-white drawings, one of which best represents the meaning of the corresponding stimulus word. The child listens to a word uttered by the interviewer and then selects one of four pictures that best describes the word's meaning.

- BNT is one of the most commonly used tests of confrontation naming. It requires subjects to provide the names of 85 drawn objects. The drawings cover a wide range of nouns, from those used very frequently (such as “house”) to those that are used rarely (such as “yoke” and “hammock”). Subjects who cannot provide the correct name within 20 sec are given a semantic cue (for example, “a type of building” for “house”); if they are still unable to give the answer after additional 20 sec, they are given a phonemic cue (for example, “hou . . .” for “house”). A positive score is attributed to every correct answer given within the first 20 sec, as well as to those given after the semantic cue [Riva et al., 2000].

- BST [Renfrew, 1969], administered in the validated Italian version [Cipriani, 2012], tests the narrative skills of children in the age range between 3 years and 6 months and 8 years and 5 months. It consists of a “retelling” task: the child is asked to listen to a story and to rehearse it using verbal description and helped by pictures. For the purpose of the present study, the test was used only as a screening tool. Therefore, the result was expressed categorically as either “presence of narrative difficulties”, when the child could not retell an intelligible version of the story, or “good narrative abilities”.

- MT is a standardized battery of tests to assess reading and comprehension skills and was specifically designed for Italian school-age children [Cornoldi and Colpo, 1998]. MT Test consists of: (a) an evaluation of reading speed measured by the time needed to read a short passage compared with a standardized measure; (b) a test of accuracy of reading, as reflected by the number of reading errors made per passage; and (c) a text comprehension test based on the ability to provide correct answers to a defined set of questions following the reading of a short story [Leverato et al., 2004]. Owing to the lack of standardized Italian tests for the assessment of narrative skills in subjects older than 9, the subtest (c) was also used for this purpose in subjects older than 9 years, by asking them to retell a story. As with younger children receiving the BST, also in this case, subjects were categorized as having “narrative difficulties” or “good narrative abilities”.

All children were also assessed by means of a custom-made questionnaire aimed to gather more in-depth information concerning different symptoms correlated with gJHM. In addition, the presence of attention deficit/hyperactivity disorder (ADHD) was checked according to DSM-IV [American Psychiatric Association, 2000]. The presence of atypical swallowing was also assessed: this condition is defined as a lingual pathological behavior, consisting of tongue pressure on the palatal and lingual surfaces of the teeth during swallowing [Melsen, 1979; Eslamian and Leilazpour, 2006].

Statistical analysis was conducted with the Medcalc software (Marienkerke, Belgium). Descriptive statistics were used for the characteristics of the samples. \( \chi^2 \) test was performed to test for differences in the frequency of symptoms between the groups. Correlation between variables was expressed by the Spearman’s ranking-order-correlation coefficients. An \( \alpha \) level of 5% was adopted for analysis.

RESULTS

Among the 41 children with DCD, 31 were boys and 10 girls (mean age 8 +/- 3 years). According to the Beighton score cut-offs, patients were subclassified in those with DCD and gJHM (i.e. DCD-H) and those with DCD but without gJHM (i.e., DCD-NH). Nineteen (46%) patients were identified as DCD-H and 22 (54%) as DCD-NH. Comparison among selected clinical characteristics between DCD-H and DCD-NH patients are summarized in Table I.

In summary, we found statistically significant differences between groups concerning frequent falls, bruising and prolonged bleeding, motor incoordination (defined as the inability to maintain a fixed posture), arthralgias and myalgias, intestinal constipation, sore hands from writing, and ADHD that further supported phenotypic clustering around gJHM in children with DCD.

In order to further scrutinize the relationship between gJHM, language disorders, and learning disabilities, a linear regression analysis was carried out and showed a positive correlation between Beighton score and ADHD \( (r = 0.59; P = 0.01) \), whereas no statistically significant correlation was observed between Beighton score and language disorders \( (r = 0.027; P = 0.86) \).

Based on the results in the speech comprehension and production test battery, patients with a language disorder were divided into three subcategories according to DSM-IV criteria:

- “expressive”, when performance was inappropriate for age in the expressive language test (BNT) and comprehension skills were normal or only mildly delayed;
- “phonological”, when they performed inappropriately for age in the PPVT test while scoring normal or mildly delayed for age in all the other tests;
- “receptive–expressive”, if LCT and PPVT test scores were lower than the...
expected mean score for age and if their performance was inappropriate in the expressive language test.

The speech/language assessment using the test battery showed significant differences in the incidence of narrative difficulties and atypical swallowing between groups (Table II).

**DISCUSSION**

In this study, we first confirmed a high rate of gJHM among children originally assessed for DCD [Kirby and Devies, 2007]. We also compared the rate of selected features, spanning from typical connective tissue features to specifically addressed neurodevelopmental attributes between a group of children with DCD and gJHM (i.e., DCD-H), and a group of non-hypermobile DCD subjects (DCD-NH). In summary, we found an excess of frequent falls (95 vs. 18%), easy bruising (74 vs. 0%), motor impersistence (89 vs. 23%), sore hands for writing (53 vs. 9%), ADHD (89 vs. 36%), constipation (53 vs. 0%), arthralgias/myalgias (58 vs. 4%), narrative difficulties (74 vs. 32%), and atypical swallowing (74 vs. 18%) in the DCD-H group compared to the DCD-NH one. Our findings suggest the existence of a highly prevalent, still poorly defined, multisystem disorder in DCD children with gJHM which could evolve in a more pronounced generalized connective tissue disorder in the later life. The eventual phenotype may be a true hereditary connective tissue disorder and, perhaps, correspond to JHS/EDS-HT. Accurate integumentary involvement was not systematically assessed in this work, because essentially conceived in a child neurology setting. Hence, we were not able to definitely confirm this hypothesis, which could represent a field for future research.

In comparison with most studies investigating the relationship between gJHM (or JHS/EDS-HT) and neurodevelopmental attributes, our observation extended such a link to language and learning difficulties. The existence of a recognizable speech impairment in patients with Ehlers-Danlos syndrome is well known in the specialized literature [Arvedson and Heintskill, 2009]. Nevertheless, evidence-based data aimed at substantiating this experience are still lacking. In this work, both groups (i.e., DCD-H and DCD-NH) showed a high rate of language disorders. More specifically, the DCD-H group displayed a significant excess of narrative difficulties with narrative competences below what is expected at their chronological age. This preliminary evidence, which needs confirmations in other studies, may share a

<table>
<thead>
<tr>
<th>Feature</th>
<th>DCD-NH (Total = 22)</th>
<th>DCD-H (Total = 19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M = (17) 77%; F = (5) 23%</td>
<td>M = (14) 73%; F = (5) 27%</td>
<td>0.92</td>
</tr>
<tr>
<td>Age</td>
<td>79 months (± 33 months)</td>
<td>87 months (± 33 months)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>1 (4%)</td>
<td>3 (16%)</td>
<td>0.495</td>
</tr>
<tr>
<td>Prematurity</td>
<td>1 (4%)</td>
<td>2 (10%)</td>
<td>0.895</td>
</tr>
<tr>
<td>Birth problems</td>
<td>5 (23%)</td>
<td>5 (26%)</td>
<td>0.922</td>
</tr>
<tr>
<td>Plagiocephaly</td>
<td>1 (4%)</td>
<td>0</td>
<td>0.941</td>
</tr>
<tr>
<td>Crooked feet</td>
<td>0</td>
<td>1 (5%)</td>
<td>0.941</td>
</tr>
<tr>
<td>Congenital hip dysplasia</td>
<td>0</td>
<td>3 (16%)</td>
<td>0.182</td>
</tr>
<tr>
<td>Neonatal UTI</td>
<td>2 (9%)</td>
<td>2 (10%)</td>
<td>0.709</td>
</tr>
<tr>
<td>Delayed toddling</td>
<td>11 (50%)</td>
<td>5 (26%)</td>
<td>0.219</td>
</tr>
<tr>
<td>Tiptoe walking</td>
<td>1 (4%)</td>
<td>5 (26%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Delayed ambulation</td>
<td>15 (68%)</td>
<td>11 (58%)</td>
<td>0.721</td>
</tr>
<tr>
<td>Clumsiness</td>
<td>14 (64%)</td>
<td>17 (89%)</td>
<td>0.119</td>
</tr>
<tr>
<td>Painful pronation</td>
<td>0</td>
<td>2 (10%)</td>
<td>0.405</td>
</tr>
<tr>
<td>Learning difficulties</td>
<td>5 (23%)</td>
<td>9 (47%)</td>
<td>0.184</td>
</tr>
<tr>
<td>Language delay</td>
<td>17 (77%)</td>
<td>12 (63%)</td>
<td>0.518</td>
</tr>
<tr>
<td>Abdominal hernias</td>
<td>0</td>
<td>4 (21%)</td>
<td>0.082</td>
</tr>
<tr>
<td>Frequent falls</td>
<td>4 (18%)</td>
<td>18 (95%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bruising and prolonged bleeding</td>
<td>0</td>
<td>14 (74%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor impersistence</td>
<td>5 (23%)</td>
<td>17 (89%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sore hands from writing</td>
<td>2 (9%)</td>
<td>10 (53%)</td>
<td>0.007</td>
</tr>
<tr>
<td>ADHD</td>
<td>8 (36%)</td>
<td>17 (89%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>10 (53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthralgias/myalgias</td>
<td>1 (4%)</td>
<td>11 (58%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ADHD, attention deficit/hyperactivity disorder; F, females; M, males; UTI, urinary tract infection.
common pathogenesis with the low motor competences in children with gJHM (or JHS/EDS-HT).

Now, it is well known the existence of an excess of defective proprioception in children with gJHM [Fatoye et al., 2009] and this is likely related to a recognizable neurodevelopmental pattern [Adib et al., 2005]. Stratified knowledge indicates that children organize language through action. In particular, Iverson [2010], and Iverson and Bradock [2011] suggested that emerging new motor skills affect infants’ interactions with objects and people, and this is relevant for development of communication and language acquisition. In the developing child with gJHM, the (presumably) generalized lack of proprioception may affect the process of organization of spatial and temporal concepts. This phenomenon could explain the observed excess of numbers and letters inversion during writing in the DCD-H group. In fact, this may stand for a difficulty in recognizing the correct spatial orientation in the “hypermobile” child. The presumed high rate of unsatisfactory orthographic competence, dysgraphia [Adib et al., 2005], and poor pen grip in gJHM children could be explained by the same mechanism. In this work, we did not systematically assess for typical satellite symptoms, such as headache, fatigue, and specific pattern of musculoskeletal pain, of JHS/EDS-HT, and did not investigate their relationship with language impairment in the DCD-H group. However, we could hypothesize that in the symptomatic child (i.e., the gJHM child also meeting JHS/EDS-HT criteria), upper limb pain, easy fatigability of upper limb muscles, and fatigue may contribute to the poor handwriting performances.

An association between DCD and attention deficit is well known by the child neurologist, who is used to attribute the diagnosis of disorder of attention and motor perception at the mixed phenotype of DCD, AD(H)D, and oppositional defiant disorder [Gibbs et al., 2007]. Accordingly, two studies found a significant association between ADHD and gJHM in children [Koldas Doğan et al., 2011; Shiarì et al., 2013]. In our work, we confirmed this association underlying the non-causal link between development of motor competence and appropriate learning skills in gJHM children. We also suggest that the presence of a (subclinical) hereditary connective tissue disorder may be an underestimated diagnosis for DCD children who also display a disorder of attention with or without an oppositional defiant disorder. The reason for an excess of ADHD in children with gJHM remains without a consistent explanation. Nevertheless, a default of the process of the organization of spatial and temporal concepts, as well as the coexistence of additional JHS/EDS-HT-related features, such as fatigue and musculoskeletal pain, could be postulated to be involved.

It is reported that low muscle tone of neck, mouth, and articulators can affect speech production, as well as swallowing in Ehlers-Danlos syndrome patients and that these subjects often have a small jaw and a highly arched palate [Shprintzen, 1997; Hunter et al., 1998; Arvedson and Heintskill, 2009]. In addition, various research groups note that the clinical absence/hypoplasia of the lingual frenulum is statistically more common in Ehlers-Danlos syndrome and JHS/EDS-HT than controls [De Felice et al., 2001; Perrinaud et al., 2007; Celletti et al., 2011]. In our study, we did not accurately assess the relationships between intraoral anatomy, tongue praxis, and speech problems. Nevertheless, DCD-H children showed a higher prevalence of atypical swallowing, a phenomenon that could be partly explained by poor tongue coordination. In this setting, we could speculate on the link between a presumed high rate of abnormal lingual frenulum in our gJHM children and atypical swallowing. Accordingly, deglutition and speech problems in gJHM (and, perhaps, JHS/EDS-HT) children may arise from the combination of short lingual frenulum and abnormal tongue pharyngeal proprioception. In turn, the evidence of a short lingual frenulum could be pathogenically unrelated to defective tongue proprioception/movement, or rather be a developmental (intrauterine) or postural (extrauterine) consequence of tongue incoordination.

In conclusion, this study highlights numerous disabling findings in hypermobile children with DCD compared to non-hypermobile subjects. Most can be treated with appropriate therapeutic plans and learning support in order to guarantee children’ adequate education and attainment of proper development. Currently, the Beighton score for gJHM, although originally elaborated by studying a pediatric population, now is not considered adequate for children. Therefore, an

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**TABLE II. Speech and Language Results in the Hypermobile (DCD-H) and Non-Hypermobile (DCD-NH) Groups of Children with Developmental Coordination Disorder.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>DCD-H</th>
<th>DCD-NH</th>
<th>$\chi^2$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>14 males; 5 females</td>
<td>17 males; 5 females</td>
<td>0.07</td>
<td>0.78</td>
</tr>
<tr>
<td>Language disorders</td>
<td>12/19</td>
<td>16/22</td>
<td>0.43</td>
<td>0.51</td>
</tr>
<tr>
<td>Type of language disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expressive</td>
<td>4/12</td>
<td>8/16</td>
<td>0.78</td>
<td>0.37</td>
</tr>
<tr>
<td>Phonological</td>
<td>2/12</td>
<td>3/16</td>
<td>3.07</td>
<td>0.88</td>
</tr>
<tr>
<td>Receptive/expressive</td>
<td>6/12</td>
<td>5/16</td>
<td>0.78</td>
<td>0.31</td>
</tr>
<tr>
<td>Narrative difficulties</td>
<td>14/19</td>
<td>7/22</td>
<td>7.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atypical Swallowing</td>
<td>14/19</td>
<td>4/22</td>
<td>12.75</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
appropriate diagnostic work-up relying on a multidisciplinary approach is necessary [Celletti et al., 2013] during which family history and JHS/EDS-HT-related symptoms should be investigated in children originally assessed for DCD. The implementation of a rehabilitation plan working on the concept of space at a bodily level (e.g., occupational and physiotherapeutic training) and at a higher thoughts level (e.g., spatial organization of the setting, organization of verbal sequences, representation of graphemes) is important, as well as a lingual motility training, especially in children with difficulties in articulation and swallowing. Such a program also needs to involve children’s families, as home treatment is known to improve the outcome [Mintz-Itkin, 2009]. In addition, strengthening meta-cognitive resources can support children to organize and control their movements, as well as their learning. This can be fostered with tools, such as computers and conceptual maps, in order to reach a better orthographic control and oral rehearsal.

REFERENCES


