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A case of Spanish language disorders with a rare genetic cause

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Abstract:
We present some tentative conclusions of our ongoing research, whose main objective is to contribute to understand how genomic disorders (and presumably, mutations in specific genes) may produce language disorders. A rare genetic anomaly which impairs speech and language production and reception (to different degrees) has been reported to one of the authors. This is a case of a girl (A) who has a balanced translocation between chromosomes 7 and 11 (t[7;11] [p13;p13]); remarkably, the affected chromosome 7 also exhibits a pericentromeric inversion with a rupture in 7p13 and 7q31. We discuss the significance of this genetic case in view of what is known so far on 7q31, a chromosomal region which encompasses some relevant loci for specific language impairment (SLI) (including the locus for FOXP2, a well-characterised “gene for language”) and autism (locus AUTS1), but which is also deleted in a rare clinical case in which language is moderately impaired. In order to explore the level of speech and language impairment of A, we have compared A’s Castilian speech to that of a girl matched for age for some general tasks. We argue that this particular case can shed some light on how linguistic tasks are disabled by the malfunctioning of specific genes.

Keywords: 7q31, genomic disorder, language impairment, Spanish

1. Clinical history
A is a female born in 1999. A was born with jaundice from which she recovered after some months. Additionally A regularly vomited an hour after feeding, a problem which decreased with frequency and ceased when she was 7. She was unable to produce comprehensible speech from the outset. Throughout her life A has been under close paediatric, educational and speech therapy monitoring. She has received two hour language therapy classes per week and special learning help throughout most of her schooling. Despite this she still has difficulties using language for communication. A requires dental braces with palatal support. However, deglutition, respiration and smiling are normal as are her hearing and locomotion. She particularly enjoys playing football and performing acrobatic movements. She is left handed and left footed. A has been wearing glasses for the last 4 years (astigmatism). Her condition has been diagnosed as Specific Language Impairment.

2. Speech and language performance
A was observed and recorded in her activities for a whole day. A, was matched for age, gender, education, social and linguistic background (bilingual Valencian and Castilian) with a subject we shall call B. A Canon FS11 camcorder was used to assess the degree of lip, jaw and facial movements used by A and B. The sound from A or B was recorded with a Sennheiser ew 100 G2 radio microphone kit, and one of the authors was recorded with a Audiotecnica 8003 microphone. Both microphones were connected to the camcorder via a DXA2S Beach Tek camcorder microphone adaptor. The recorded speech has been analysed using a Praat analyser which gives detailed measures of pulses, formants, intensity, pitch, spectrum and time in ms. A was recorded at the school in two occasions: firstly in one conversation with one of the authors and secondly in one session with the school speech therapist. A was also recorded at another speech therapy session. B was recorded at a paediatric centre. A was observed in all her activities that day and notes were taken on her behaviour and language performance with her schoolmates, teachers and family.

Five tests were administered to both subjects. Two conversation topics (school lessons and languages used to communicate), one morphological test (8 verbs combined with yesterday, today and tomorrow),
one syntactic test (asking to complete the arguments and adverbial information for a verb), one reading comprehension test (listening to a 45 word passage in order to answer 6 yes/no questions), and one narrative test (listening to a 61 word passage in order to summarize the content with their own words). In each, A failed not only at the integration and production of necessary elements at the phonological, morphological or syntactic levels, but also at producing the correct timing of those which were uttered. A also failed to answer correctly the questions for the comprehension test correctly and failed at coherently narrating coherently the short passage she had to listen to. B did not fail any of the tests nor the comprehension or narrative test.

Under spontaneous verbal communication, compared to B, A failed to correctly sequence articulations. In conversation, when A and B retold what they had done at school that day, A gave a list of subjects showing basic failures in motor planning among them: (i) [enmucçacçó] for [eduakaþjón] “education”, with anticipation of final nasal and concomitant repetition of nasal as initial [mu] (García-Bellido 2005), avoidance of palatal interval [j] in [CjV] (García-Bellido 2000, 2003) with a concomitant synchronization and replication of palatalization and affrication [cc]; (ii) failure in motor integration in one prosodic sequencing: [balén] [ðjáno] for [balenþjáno] (‘Valencian’), with concomitant addition of glottal activation in the first fragment which produced iambic stress and raising intonation (García-Bellido, 1997). B instead elaborated syntactic expansions for each subject and she did not show any (perhaps motor planning) errors. Under elicitation and repetition, A, at random, had better performance. Sibilants produced dissimilations when sequencing one after the other: [pisíãña] for [pisöðíña] (‘swimming pool’). Laterals were frequently replaced by rotics: [peʃo] for [pelo] (‘hair’). Palatalizations and nasalizations were produced in imitation (given [kaʃpíntèrò] (‘carpenter’), A imitated [naŋapèrò]) (cf. Shriberg et al., 2006).


At the syntactic level, A failed, under spontaneous speech, to integrate incorporating a complete locative relative clause. For instance, A was asked what she was looking for. A produced as an answer: [lakaxita amo/andando] (‘the small box and eating’) for roughly: “la cajita // donde guardo el aparato mientras estoy/almorzando///” (“The small box // where I keep the braces while I am/ eating///”). The entity ‘box’ and the last element, the time adverbial gerund ‘eating’, were connected by an interval made of a paratactic palatal connector [l] (‘and’) (cf. López García, 1999), while the rest of the relative clause construction was omitted. A showed systematic failures at expressing a spontaneous idea coherently. For instance, in order to express that she did not go to football training because she had to get ready for a performance as the queen of the local festival (“fallera mayor”), she needed to combine two simultaneous events in the past and connect them by a logical exclusive relation: [A (`fallera')-but-not-B (football)]. Her construction was: “Un poquito antes pero mi falla en fallera mayor, mi, yo... mi... con fallera en fútbol” (‘a little before but my falla in fallera mayor, my, I... my... with fallera in football’). Further attempts were hampered by repetitions, interruptions, additions, omissions and by an inability at integrating the whole in a short time. A request was expressed as declarative [aβaɾes] for [aβær] (‘you open’) and no exclamative constructions were produced. In the syntactic test under elicitation, A could not form a predicate with all its arguments: “[pësaenlabähkula]” for “pesa uvas en la báscula” (‘weighs in the scale’ for ‘weighs grapes in the scale’). B created complete predicate-argument sequences with relative, subordinate and coordinated clauses at ease.
3. Other linguistic/cognitive impairments

A was reported by school and parents to have tantrums for minor issues. This was confirmed in our inspection. She showed competitiveness with schoolmates. She is reported by her family to be emotionally detached with them and to perform rituals when tidying up her toys. Her behaviour is not aggressive. However, A showed very developed drawing skills which should be further investigated and evaluated by special tests.

Additionally, problems in writing were found in A’s performance. *Flor ‘flower’* was written as *{fror}, {for}, {folor}, {fro}* in a sequential attempt to get the right spelling; *suave ‘soft’* as *{sueva}, áspera ‘rough (fem.)’* as *{espera}, pared ‘wall’* as *{pade} and zapatilla ‘slipper’* as *{zapaticha}. A could not always understand what she read. Reading just isolated sequences such as *{plátano} ‘banana’* would be pronounced as *[paɾˈatano]. B did not show any problems while reading or writing.

Being this a first exploratory study, where no standard protocols have been administered to measure the level of linguistic deficit compared to a non affected population, the results obtained merely confirm that A has language deficits very similar to those already found in other phonological and morphological studies of individuals where the *FOXP2* gene has been altered (Shriberg *et al.*, 2006, for the two members of the TB family; Watkins *et al.*, 2002 and Vargha-Khadem *et al.*, 1995 for the family KE). More controlled linguistic and non-linguistic tests will be administered using if possible a bigger sample of non affected individuals.

Since neither intelligence nor non-linguistic tests have been performed yet at this age, this case cannot be definitively assessed as solely SLI.

4. Cytogenetic analysis

A is characterised by the presence of a reciprocal (or balanced) translocation between chromosomes 7 and 11 (*t*[7;11] *p13; p13*). In chromosome 7 a pericentromeric inversion, which affects the fragment 7p13-7q31 has also been produced.

5. Discussion

Although it is possible that some functional gene could have been affected by the ruptures in 7p13 and 11p13, the fact that the third rupture point corresponds to the 7q31 region deserves to be highlighted, especially when considering A’s oromotor and language impairments. This region coincides with the *locus* SPCH1, which corresponds to the *FOXP2* gene (Fisher *et al.*, 1998; Lai *et al.*, 2001). This gene codes for a transcription factor which seems to be involved in the specification of neural identity and/or neural function required for the organisation and/or activity of specific cortico-thalamic-striatal circuits associated with motor planning, sequential behaviour and procedural learning.

The different expressive difficulties derived from the mutation of this gene have been indistinctly described as orofacial dyspraxia (or developmental verbal apraxia) (Vargha-Khadem *et al.*, 1995) or as a spastic dysarthria which would co-occur with verbal dyspraxia and residual errors during development (Shriberg *et al.*, 2006). However, affected individuals show linguistic dysfunctions which surpass strictly articulatory aspects. These are: (i) a working memory deficit in storing relevant phonological information (or perhaps in producing sequential articulation of phonologically relevant units); (ii) a low level of lexical knowledge; (iii) a diminished capacity (in quantitative and qualitative terms) to retrieve lexical elements; (iv) less capacity for morphological and morphosyntactic integration; and (v) problems of morphological generation with respect both to nouns and verbs, which affect regular and irregular formation and which usually lead to processes of overgeneralization (mainly verbal) (Gopnik and Crago, 1991; Vargha-Khadem *et al.*, 1995; Watkins *et al.*, 2002). The characteristic symptoms of spastic dysarthria include (and exceed) those associated with verbal dyspraxia and, in fact, both disorders seem to have a slightly different etiology. Spastic dysarthria could be caused by a breakdown of the first of two steps needed for pre-programming motor control required by articulation. This is a key step for correctly integrating subtasks of different articulators into a coherent whole (Klapp, 1995). Verbal dyspraxia seems to be a dysfunction of the second of the two steps which encompasses the process of programming itself. Programming entails sequentially organizing the different tasks needed for articulation, including the
specification of the appropriate muscular parameters for this articulation, such as the force and the speed of response of the implicated muscles (Klapp, 1995). It has been suggested therefore that the term “sensorimotor disorder” (Shriberg et al., [2006] following to McNeil [1997]) would be more appropriate in order to denote the general nuclear deficit associated with the different mutations of the FOXP2 gene. As their different phenotypic manifestations seem to put forward, these mutations might have dissimilar effects at the level of proteins, regulators and neurons (for a review see Benítez-Burraco, 2008a; 2008b). The articulatory, morphological, and syntactical deficits found in A’s performance are coherent with the findings in other cases where FOXP2 has been affected (Gopnik and Crago, 1991; Watkins et al., 2002; Shriberg et al., 2006).

On the other hand, deletions of different extension which affect this region produce equally important expressive dysfunctions, which from a clinical viewpoint have been described, broadly, as orofacial dyspraxia. This is in particular the case of the deletion of (i) region 7q31.2-7q32.3, which produces a phenotype encompassing facial dysmorphism, mental retardation, and absence of language (Sarda et al., 1988); (ii) region 7q31.2-7q32.2, which produces psychomotor delay and some mental retardation (Zeesman et al., 2006); (iii) region 7q31.1-7q31.31, which produces facial dysmorphism, slight mental retardation and developmental verbal dyspraxia (Lennon et al., 2007); and (iv) a fragment of 4.4 Mb belonging to the region 7q31.3 which contains some genes which are expressed in the brain and which gives rise to a type of language disorder which affects mainly the expressive component (Tyson et al., 2004), with the added effect that the interruption of this region by a translocation event causes problems with sequencing, and with retrieval of lexical elements during production, but also causes articulatory difficulties described as developmental verbal dyspraxia (Lai et al., 2000; Warburton et al., 2000). Most of these patients are incapable of voluntarily laughing or sneezing. Additionally, different balanced translocations between 7q31 and other chromosomes have been described. These give rise to speech impairments, like the one recently reported by Kosho et al. (2008), which involves 7q31 and 10p14. At the same time, the 7q31 region seems to correspond equally to a locus for SLI (Newbury et al., 2002). These individuals show an abnormal ontogeny with respect to linguistic competence in absence of non linguistic causes, such as insufficient exposure to linguistic stimuli during social development, general mental or cognitive retardation, neurological dysfunction or auditory problems (Bishop and Leonard, 2000; Leonard, 1998). This locus does not seem to correspond to the FOXP2 gene (O’Brien, 2003). Simultaneously, the 7q31 region has also been associated with autism (locus AUTS1) (Folstein and Mankoski, 2000; Wassink et al., 2001). Again, locus AUTS1 does not seem to overlap with the coding sequence of the FOXP2 gene (Newbury et al., 2002), although it could overlap with some regulatory region or with the sequence of another different gene, such as some of those contained in the fragment identified by Tyson et al. (2004) or even genes MET, ST7 or WNT2, previously related to autism (for a review see Benitez-Burraco, 2008c). One should perhaps pay attention to the fact that the linguistic profile of the autism subtypes in which linguistic competence dysfunction is not reduced to the pragmatic component (cf. Rapin and Dunn, 2003) seems to be similar to the linguistic profile which characterizes SLI, particularly with respect to the deficits observed in phonological and morphological processing (Tager-Flusberg, 2006).

Finally, it should be underlined that the contiguous region 7q32 has also been associated to both dyslexia (Kaminen et al., 2003) and autism (IMGSAC, 1998). Considering the relative imprecision concomitant to this kind of cytogenetic analysis and association/linkage studies, it seems plausible that region 7q31-q32 could contain one common genetic determinant for (or different genes relevant to) SLI, dyslexia, and autism.

The linguistic (and cognitive) profile of A points to the possibility (which has to be further explored) that her language/cognition impairments can be due specifically to the functional inactivation of a gene contained in this region.

6. References
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Este volumen recoge la mayor parte de las comunicaciones presentadas al II Congreso Internacional de Lingüística Clínica (Madrid, UAM, 11-13 noviembre 2009), distribuidas en las diversas áreas temáticas del congreso: Fonética y Fonología Clínicas, Gramática Clínica, Lexicología y Semántica Clínicas, Pragmática Clínica, Sociolingüística Clínica, Descripción, evaluación e intervención en las alteraciones del lenguaje, Lenguaje y cerebro y Adquisición y desarrollo del lenguaje desde la lingüística clínica: L1 y L2.

Dada la notable acogida del congreso, dentro y fuera de nuestras fronteras, las comunicaciones aparecen mayoritariamente en inglés, pero también en español. Lingüísticamente, es de destacar la gran riqueza tipológica de las lenguas analizadas; desde un punto de vista clínico, sobresalen las aportaciones sobre enfermedades raras, como el síndrome de Williams, que se suman a los estudios sobre aphasías, Trastorno Específico del Lenguaje, y otros déficits que afectan al lenguaje.

El interés y la calidad científica de los trabajos presentados convierten esta recopilación en un paso importante, no sólo en el desafío de la Lingüística ante la aplicación clínica, sino en la difusión exterior de la Lingüística Clínica española, y el afianzamiento en España de la Clínica como una de las aplicaciones relevantes de la Lingüística.

This volume collects the majority of the papers accepted for the II International Clinical Linguistics Conference (Madrid, UAM, November 11, 12, 13, 2009), arranged by the various thematic topics of the congress: Clinical phonetics and phonology, Clinical grammar, Clinical linguistics and lexical-semantic aspects, Clinical linguistics and pragmatics, Clinical sociolinguistics, Description, Assessment and treatment of language disorders, Language and the brain, Language acquisition and development, and Clinical Linguistics: L1 and L2.

Papers are in either Spanish or English, the congress’s official languages, owing to the great response to the Conference both inside and outside our country. In this regard, the richness of linguistic typology under analysis is highlighted, as well as the new views on aphasias, genetic syndromes, Specific Language Impairment, etc.

The interest and scientific rigor of these papers make this volume an important addition to the literature, for promoting Spanish Clinical Linguistics outside of Spain, as well for consolidating Clinical Linguistics within Spain as one of the most important applications in the field.