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Short Communication

Behavioral and neurobiological correlates of childhood apraxia of speech in Italian children ☆

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ABSTRACT

Childhood apraxia of speech (CAS) is a neurogenic Speech Sound Disorder whose etiology and neurobiological correlates are still unclear. In the present study, 32 Italian children with idiopathic CAS underwent a comprehensive speech and language, genetic and neuroradiological investigation aimed to gather information on the possible behavioral and neurobiological markers of the disorder. The results revealed four main aggregations of behavioral symptoms that indicate a multi-deficit disorder involving both motor-speech and language competence. Six children presented with chromosomal alterations. The familial aggregation rate for speech and language difficulties and the male to female ratio were both very high in the whole sample, supporting the hypothesis that genetic factors make substantial contribution to the risk of CAS. As expected in accordance with the diagnosis of idiopathic CAS, conventional MRI did not reveal macrostructural pathogenic neuroanatomical abnormalities, suggesting that CAS may be due to brain microstructural alterations.

1. Introduction

Childhood apraxia of speech (CAS) is a subtype of pediatric speech-language disorder, defined by the American-Speech-Language-Hearing-Association (2007) as "a neurological childhood disorder in which the precision and consistency of movements underlying speech are impaired in the absence of neuromuscular deficits". CAS is usually interpreted as a speech motor disorder, whose core deficit involves the planning and/or programming of the spatiotemporal parameters of movement sequences (ASHA, 2007).

Children with CAS display reduced speech timing and sequencing skills and show particular difficulties in dynamic transitions between articulatory postures and in combining smaller units of movement into larger ones. Early oromotor and speech acquisition difficulties in CAS may stem from the lack of a probable innate ability to form systematic mappings between articulatory gestures and their auditory effects (Maassen, Nijland, & Terband, 2010). In a recent study Shriberg, Lohmeier, Strand, and Jakielski (2012), suggested that CAS is a multi-level disorder in which both planning/programming (transcoding) and auditory- perceptual (encoding) deficits are involved, together with memory processes.

According to the ASHA consensus criteria (ASHA, 2007), three features are characteristic of CAS (a) inconsistent errors on consonants and vowels during repeated productions of syllables or words, (b) lengthened and disrupted co-articulatory transitions between sounds and syllables, and (c) inappropriate prosody, especially in the realization of lexical or phrasal stress. Other features include reduced phonetic inventory, multiple speech sound errors, disfluency and unintelligibility (ASHA, 2007).

In spite of increasing interest in the study of this disorder, as recently indicated by Murray, McCabe, Heard, and Ballard (2015), differential diagnosis of CAS from other Speech Sound Disorders remains problematic because of the lack of validated assessment protocols. Moreover, after extensive behavioral, neuroimaging and genetic studies of the KE family (whose affected members had severe verbal dyspraxia and a mutation in the FOXP2 gene,

☆ **Statement of significance to neurobiology of language:** This manuscript investigates behavioral and neurobiological characteristics of idiopathic childhood apraxia of speech. The goals were to explore the pattern of relationships between speech and language symptoms of CAS and their etiological correlates, in order to gather information on possible clinical markers of the disorder.

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Vargha-Khadem, Gadian, Copp, & Mishkin, 2005), very few researches on CAS simultaneously addressed these three aspects.

As for etiology, apraxia of speech may be symptomatic, cryptogenic or idiopathic. Symptomatic and cryptogenic CAS can be secondary to known neurological pathologies of a metabolic (as in galactosemia, cfr. Shriberg, Potter, & Strand, 2011 and in creatine transport deficiency, cfr. Battini et al., 2007), epileptic or genetic nature (as in children with Down syndrome). Idiopathic CAS can be the only symptom present in otherwise healthy children, occurring as a neurogenic Speech Sound Disorder whose etiology and neural correlates remain poorly understood.

From a genetic point of view, landmark studies on a single large family (the KE family, cfr. Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001), in which about half of the members were affected by orofacial and speech apraxia, identified a mutation in the FOXP2 gene located in chromosome 7q3 (Hurst, Baraitser, Auger, Graham, & Norell, 1990). Subsequently, other cases with de novo and familial FOXP2 mutations have been described. However, the results of studies by MacDermot et al. (2005) and Laffin et al. (2012) on larger populations showed a low prevalence of FOXP2 alterations (2% and 4% respectively). Moreover, using Array-Comparative Genomic Hybridization analysis (a-CGH), Laffin et al. (2012) found several copy-number variations (on chromosomes 2, 13 and 14) in 12 of their 24 patients. Other chromosomal abnormalities have been identified with a-CGH analysis (12p13.33, Thevenon et al., 2013; 16p11.2 microdeletion, Fedorenko et al., 2015; Raca et al., 2013; 2p15p16.1 microdeletion, Peter, Matsushita, Oda, & Raskind, 2014,) and with Whole Exome Sequencing analysis (gene alterations in chromosomes 3, 6, 7, 9, 17, Worthey et al., 2013).

Regarding neural correlates, CAS rarely occurs in children suffering from congenital focal brain lesions of the left hemisphere (Chilosi et al., 2008). This is different from acquired adult apraxia of speech, that is generally due to left hemisphere lesions. According to adult models of speech production, planning and execution of speech movements may rely on distinct, though interlinked, neural circuitries (Liégeois & Morgan, 2012; Ogar et al., 2006). Speech planning could involve the supplementary motor area, anterior insula, dorsolateral frontal cortex and superior cerebellum; while speech execution could be subserved by the primary motor cortex, extrapiramidal system, thalamus and inferior cerebellum. Neuroimaging investigation of affected KE family members, revealed structural and functional abnormalities in a vast cortical-subcortical network including perisylvian and rolandic cortices, caudate nucleus, inferior frontal gyrus and supplementary motor area (Liégeois, Morgan, Connelly, & Vargha-Khadem, 2011; Vargha-Khadem et al., 2005). However, these findings cannot be generalized to every case of CAS. As reported in a recent review by Liégeois and Morgan (2012), in the past 13 years only twelve articles describing 45 children with CAS were accompanied by MRI investigations, which did not reveal any significant abnormality in around 60% of cases. Research on neurobiological markers of idiopathic CAS is still an emerging field for which no conclusive information is available. Moreover, very few studies have analysed the clinical, genetic and neuroanatomical correlates of this disorder in relative large populations of patients and, in particular, no data on Italian-speaking children are available.

In this study we investigated the clinical, genetic and neuroradiological characteristics of 32 Italian children affected by idiopathic CAS. Our goals were to explore the patterns of relationship between speech and language symptoms of CAS and their etiological correlates, in order to gather information on possible clinical markers of this disorder.

All children underwent a comprehensive assessment that included neurological and speech and language evaluation, genetic testing (a-CGH) and structural MRI.

2. Results

2.1. Clinical and neurobiological investigation

No child presented neurometabolic abnormalities at biochemical testing.

At neurological assessment, gross and fine motor organization was below age expectation in 65.5% of children. Evaluation of cognitive abilities (WPPSI and WISC-III or IV) showed a mean Performance IQ of 94.5 (SD 16.4; range 57–107). PIQ was in the normal range in 23 out of 32 children and in the borderline range (70–85) in 7; only 2 subjects had a mild cognitive deficit.

2.1.1. MRI findings

Structural brain MRIs revealed only minor brain abnormalities: aracnoid cysts (4 cases), lower position of cerebellar amygdales (4 cases), retrovermian space enlargement (2 cases), partial thinning of corpus callosum (2 cases), frontal venous dysplasia (1 case). Proton MR spectroscopy was normal for the entire sample.

2.1.2. Genetic findings

An intra- and inter-familial heterogeneity was observed in 70% of cases, in which a CAS proband had parents or relatives with a positive history of language disorder or dyslexia, or both. Six subjects presented an alteration at a-CGH with one patient (TF) showing a de novo complex genetic abnormality. In this patient, a duplication in chromsome 9 (9p22.1p24.3) involving a very large portion (18 Mb) of the terminal part was associated with a 6 Mb deletion affecting the long arm of chromosome 4 (4q35.1.q35.2). In three cases, genetic abnormalities were inherited from one parent: one female had an interstitial duplication in chromosome 8 (8p23.1), also present in her father; in a male and in his father a microdeletion in chromosome 1 (1q21.1) was found; another male child and his mother had an interstitial duplication in chromosome 5 (5p13.3). Two heterozygous twins presented an interstitial duplication in chromosome X (Xq21.1); a-CGH analysis of their parents is still under investigation.

None of the parents showed signs of CAS (they received a normal education and all were currently employed).

2.2. Case history and behavioral assessment

2.2.1. Parents' report

Pre-perinatal history was normal in 23 children; some transient problems during pregnancy or delivery were reported in the remaining 9, but none suffered from severe fetal or neonatal complications. Fourteen children (43%) suffered from recurrent otitis media during the first years of life, but none had persistent auditory deficits.

Based on parental reports, all children presented severe speech and language delay characterized by:

- Absent (10 cases) or quantitatively reduced and qualitatively abnormal babbling (22 cases), with delayed onset (mean age 14.3 months, SD 8 months; range 9–30 months) and sporadic production of a very restricted number of speech sounds.
- Delayed emergence of first words (mean age 25.9 months, SD 11.6 months; range 12–48 months).
- Very slow increase of vocabulary size with delay in acquisition of the first 50 words (mean age 54.6 months, SD 14.1; range 30–83 months) and late emergence of combinatory speech (mean age 54.5, SD 13.7; range 30–83 months).
- High percentage of unintelligible speech during preschool years. The difference between the proportion of unintelligible speech for family members (mean 60%) and unfamiliar adults (mean