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COGNITIVE PROFILE IN WILLIAM SYNDROME: A CASE STUDY

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Introduction

Williams Syndrome (WS), described for the first time by J.C.P. Williams in 1961 (Williams *et al.*, 1961), is a rare neurodevelopmental disorder, which occurs 1 in 20,000 live births, and is caused by a submicroscopic delection in the band q11.22-23 of chromosome 7. Several genes located in this deletion area are implicated, including the gene for elastin, which is responsible for the congenital cardiac problems. Other genes involved in the deletion include LIM-1 Kinase, WSCR1-5, RF2C, FZD3, GTF2IRD1, GTF2I and syntaxin 1A (Korenberg *et al.*, 2000) and may be associated to other clinical features. Indeed, Hirota *et al.*, (2003)

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found that the genes GTF2IRD1 and GTF2I contribute to deficits in visual spatial functioning.

Patients with WS have an unusual phenotype, which includes a distinctive profile of physical, medical, neuropsychological and neuroanatomic characteristics. Their typical physical characteristics include facial dismorphology (such as an elfin-like face, depressed nasal bridge, stellate iris pattern, flared nostrils, wide mouth with prominent lips and irregular dentition) and a specific clinical phenotype, which includes cardiovascular defects like supravalvular aortic stenosis or pulmonic stenosis, calcium metabolism abnormalities, hypertension, failure to thrive in infancy and delayed development. They usually have poor motor coordination, muscle tone disorders (hypertonia) and articulation problems. They also suffer from hyperacusia, an extreme sensivity to sound, although this tends to become less problematic with development (Karmillof-Smith *et al*., 1995; Lenhoff *et al*., 1997; Bellugi *et al*., 1999a; Bellugi *et al*., 2000; Galaburda *et al*., 2003; Semel and Rosner, 2003).

Individuals with WS also display distinct behavioural patterns, characterised by an excessive social behaviour, with a strong impulse towards social contact and affective expression (Bellugi *et al*., 1999b; Jones *et al*., 2000). They exhibit a hypersociability and outgoing nature, which differentiates them from other neurodevelopmental disorders. Some authors suggest the involvement of a genetic predisposition in the expression of hypersociability (Doyle *et al*., 2004). However, they may evidence some disadaptive behaviours like hyperactivity, propensity toward inattention, and even social withdrawa, daily living skills being the weakest adaptive ability (Greer *et al*., 1997).

Patients with WS also present a unique cognitive phenotype, with a mildly to moderately retarded intelligence (mean IQ is 55, standard deviation 11, and range between IQ 40 and 90) with a significant variability in intellectual functioning within this population (Bellugi *et al*., 1999a; Bellugi *et al*., 2000; Bellugi *et al*., 2001) and is associated with generalised difficulties in general problem solving, arithmetic, planning as well as typically being unable to achieve fully independent living (Bellugi, *et al*., 1994). Despite their low IQs, individuals with WS display characteristic patterns of cognitive performance with peaks and valleys of abilities. Specially striking is a well-documented dissociation between severely impaired visuospatial cognition (which is severely impaired, particularly at the level of global organisation), and face processing abilities (Rossen *et al*., 1995; Farran, *et al*., 2001) as well as linguistic abilities that are relatively preserved. Indeed, several studies show evidence for a proficient and creative use of specific aspects of expressive language (use of evaluation devices for enriching and engaging audience) which contrast with mental retardation and other cognitive impairments (Bellugi *et al*., 1994; Bellugi *et al*., 2000; Bellugi *et al*., 2001). Individuals with WS are also highly verbose in vocabular production of typical and atypical words (Bellugi *et al*., 1999a). However, several authors have been claiming that this dissociation is basically an experimental artefact, and that more detailed analysis of the socio-affective and linguistic domain will show evidence or subtle deficits in this profile (Kamirloff-Smith *et al*., 2003). Thus, in a study about narrative

skills in WS, Reilly *et al*. (2004) found that they have lower performance on measures of narrative structure, but proficiently use the social aspects of narratives. Also, Gonçalves *et al*. (2004) found that in their study individuals with WS had a poor performance on narrative tasks (structure, process and content), suggesting that given the multimodal and integrative nature of the narrative, including highly complex elements (not only structural, but also process and content elements) it is unlikely that all dimensions of narrative production are spared in WS (Gonçalves *et al*., 2004).

The neuroanatomic profile of WS emerging from initial neuroimaging studies is beginning to contribute to the understanding of the brain's organisation, helping to bridge the neuromorphological pattern of this disorder with the knowledge of cognitive phenotype. Thus, the relative sparing of frontal and cerebellar structures in individuals with WS might contribute to their relatively good linguistic competence and privileged socio-affective development. An enlarged cerebellar vermis (Schmitt *et al*., 2001c) in particular may be involved in more complex processes at the emotional and social behaviour level. Also, the increased volume of the superior temporal gyrus, an area that contains the auditory system and the auditory association areas that form part of language networks, are well documented in literature (Galaburda and Bellugi, 2000; Bellugi *et al*., 2000; Reiss *et al*., 2001).

Neuroanatomical studies of the WS brain have reported a distinct morphology when compared to normally developed individuals and have shown differences in the global cerebral shape (Schmitt *et al*., 2001b) - the overall length of both cerebral hemispheres is significantly smaller (the brain volume could be disproportionately reduced in particular regions like the parietal-occipital region). In another study Schmitt and colleagues (2001a) measured the corpus callosum and its subdivisions and found that the total midsagittal corpus callosum area was reduced in WS individuals relative to the control group, more specifically the posterior regions of the CC (istmus and splenium). In an exhaustive study with magnetic resonance imaging (MRI), Reiss *et al*., (2001) studied a 14-subject group with WS and a matched normal control group and found that WS have: decreased overall brain and cerebral volumes (13%); relative preservation of cerebellar and superior temporal gyrus volumes; disproportionate volume reduction of the brain stem (20%); significant differences in relative grey and white matter tissue proportions between groups: a relative sparing of their cerebral grey matter volume when compared to controls and disproportionate reduction in cerebral white matter volume; abnormal patterns of asymmetry in the occipital lobe (abnormal leftward predominance of grey matter); grey matter volume of the superior temporal gyrus (STG) in individuals with WS were proportionally larger compared to controls.

Given this uneven cognitive, behavioural and neuroanatomic profile, our aim is to describe a WS case, to explore clinical evidence for this cognitive dissociation repeatedly reported in the literature. In order to do this, we used a broad neuropsychological battery of tests and analysed the data to design an individualised rehabilitation programme, the focus of which was to improve areas of weak performance.

Methodology

Patient

The patient (MMP), a 13 year old boy, is the youngest of three children from a family characterised by a low socioeconomic level. He was born by caesarean section. In terms of developmental milestones he began to say the first words when he was 18 months old and started walking after 2 years, reading at 6 and began to write when he was 7 years old. At the age of 12 he was diagnosed with Williams Syndrome by fluorescent in situ hybridisation (FISH). At the assessment time, he was in 5th grade (adapted curriculum) and had failed twice (1st and 3rd grade). The patient showed limitations in performing daily life activities (to button up clothes, to tie shoe-laces) and revealed several cognitive deficits, particularly in attention and concentration, fine motor skills, motor coordination and visuospatial cognition.

Instruments

Neuropsychological assessment allows the clinician to ascertain the patient's cognitive strengths and weaknesses, the implications of such deficits and the rehabilitation needs of the patient (Benett, 2001). In this specific genetic syndrome, knowing the patient's strengths and weaknesses allows the possibility of designing specific individualised rehabilitation programmes in order to preserve the strengths and improve the weaknesses (Braden and Obrzut, 2002).

Indeed, given the complexity and diversity of mental abilities that need to be clinically addressed in WS patients, several neuropsychological and cognitive instruments were used with this patient. The evaluation instruments used were the following:

Wechsler Intelligence Scale for Children – R (WISC-R)(Wechsler, 1974) - It is an instrument allowing a basic review of general cognitive functions providing initial clues for the existence of altered mental abilities (Lezak, 1995). This instrument gives information about the overall level of intellectual functioning (IQ). It is composed of 12 subtests, six verbal and six performance oriented. Each subtest delivers a scaled score which may range from 1 (lowest) to 19 (highest). The verbal and performance tests give, respectively, a verbal IQ and performance IQ score. The full-scale IQ score is calculated from the sum of all the individual test scores.

Narrative Elicitation Task - in this narrative task, the patient was presented with the 24-page wordless picture book, *Frog, where are you?* (Mayer, 1969), and was asked to tell the story. Because it is a wordless book and given the multiplicity of processes, contents and structural elements suggested by the images, this book provides a rich context for language production and has been used extensively in several studies of linguistic skills among typically and atypically developing populations (Reilly *et al.*, 2004; Gonçalves *et al.*, 2004). The child narrative was videotaped for transcription purposes and analysed using 3 standard measures (each one with 4 dimensions evaluated on a five point Likert scale): structural coherence, process complexity and content diversity (Gonçalves *et al.*, 2002a,b,c).

Controlled Oral World Association (Benton and Hamsher, 1989) – this is a verbal fluency test and evaluates the changes in the speed, verbal spontaneity

production and verbal fluency. This test studies the oral production of spoken words beginning with a designated letter (F, A, S) and a category naming trial (animals) within a time limit (1 minute). Fluency problems may be associated with difficulties in speech, reading and writing. The test is sensitive to frontal executive dysfunctions and slight alterations in semantic memory (Spreen and Strauss, 1991).

Toulouse Piéron Test (perceptual and attention test) (Toulouse and Piéron, 1986) – this is a cancellation test and requires visual selectivity at fast speed on a repetitive motor response task. The test gives information about concentration and monotony resistance abilities, as well as perceptual quickness and continued attention skills. Lower scores can reflect the general response slowing and inattentiveness.

Trail Making Test (Reitan, 1958) – this test, originally part of the Army Individual Test Battery, is used to assess visual conceptual and visuomotor tracking (Lezak, 1995). It is a test of speed for visual search, attention, mental flexibility and motor function. It has two parts, A and B. Part B requires more information processing ability than part A and is clearly the more sensitive part of the test (Spreen and Strauss, 1991). Problems in visual scanning and tracking gives the examiner an idea of how effectively the patient responds to a visual array of any complexity; follows a sequence mentally; deals with more than one stimulus or thought at a time or is flexible in shifting the course of an ongoing activity.

California Verbal Learning Test for Children (Delis *et a*l., 1994) - Spanish version: this is a memory test in which the participant reads a shopping list (list A) of 15 words from three categories (fruit, clothing and school material) presented to the individual in 5 trials. The participant is then asked to recall as many words as possible in each trial. Following the fifth trial of list A, an interference list of 15 words is read (list B) also from three semantic categories (animals, furniture and fruits). After recalling these words, the individual must recall list A words, first freely (short-delay free recall) and then cued by semantic category (short-delay cued recall). After a 20-minute delay, free and cued recall of list A are again elicited (long-delay free recall; long-delay cued recall). The last task is a recognition memory task, in which the individual is read a list of 45 words (15 words from list A and 12 from list B including words not belonging to these lists) and asked to identify if the word was from list A. It also gives information about the number of false positives (discrimination index), intrusion errors and perseverations (Nichols *et al.*, 2004). This instrument provides important information about the individual's use of learning strategies and their effectiveness (Lezak, 1995). Responses were scored using the TAVECI normative data and converted into *z* scores (Benedet *et al.*, 2001). Given the multitude of variables performed by this test, we only present those which are central to learning and memory.

Rey – Osterrieth Complex Figure Test (Rey, 1959) – recall and copy administration: this test requires the person to copy a complex figure without a time limit, and evaluates the use of organisation and planning strategies in problem solving and visuoconstructive ability. Then, after 30 minutes, the person is asked to repro-

duce the same figure, from which the examiner evaluates the individual's ability to recall non-verbal material.

Discussion

The patient showed a serious impairment in general cognitive functioning. In the Weschsler Intelligence Scale for Children – R, he had a verbal IQ 53, performance IQ 46 and full scale IQ 42, falling in the range of mild to moderate retardation, consistent with the research literature data (Bellugi *et al.*, 1994; Bellugi *et al.*, 1999a). However, the verbal IQ is slightly superior to the performance IQ.

The overall pattern of cognitive functioning illustrates the typical model of visuospatial deficits shown in this syndrome. Aside from being seriously impaired in the various areas of visuomotor performance (visuospatial construction, spatial orientation, fine motor skills and visual memory), these deficits tend to interact and accumulate. Indeed, he demonstrated spatial deficits and performed poorly in visuospatial tasks, Rey – Osterrieth Complex Figure Test – copy administration, where he had a score at the 10th percentile. This is consistent with review studies, which report that visuospatial abilities in WS are collectively poor (Farran and Jarrold, 2003).

These difficulties shown by the patient have implications in performance in visual memory tasks (score on Rey – Osterrieth Complex Figure Test – recall administration was at 1 percentile). He had severe difficulties in visuospatial memory and also in verbal memory measures. Indeed, he presented a moderate deficit in learning and retention skills (z scores on List A was -2 and on List B Recall was -1.5), although there was a normal use of serial strategies in the recovery of the learned items in the California Verbal Learning Test (z = -1 for serial strategy in free short-term recall and z = 1 for serial strategy in free long-term recall). The cued recall facilitates the information recovery process (normal range) when compared with free recall (short term and long term). There is a pronounced primacy effect, which may be associated with a proactive interference of the first presented words, making difficult the acquisition process for new items. The patient also demonstrated a poor discrimination of relevant from irrelevant information (z = -2.5 for discrimination index) and in recognition tasks he performed weakly, suggesting some difficulties in the information recovery process (z = -2.5). Indeed, Nichols *et al.* (2004) studied the profiles of verbal learning and memory performance in 5 groups of children (typically developing children, specific language impaired, early focal brain damaged, children with Williams Syndrome and with Down Syndrome) and found that verbal learning and memory abilities in WS are poor compared to controls, even when their performance is scored according to mental age.

Initial studies show that the linguistic abilities of WS patients are relatively unaffected (Bellugi *et al.*, 1994; Bellugi *et al.*, 1999a; Bellugi *et al.*, 2000). In fact, in verbal subtests of the WISC-R, the patient had a superior performance (verbal IQ was 53 and he performed well in a vocabulary subtest (22) relatively to performance subtests (performance IQ was 46 and in the block design subtest he scored only 1). However, linguistic abilities were questionable when analysing his performance on language and verbal fluency tests (all scores were below the mean standard in the Fluency Verbal Test, he

had a score at the 20th percentile and in the category test he only named 11 animals). Also, the overall performance on narrative tasks was poor, in contrast to the high narrative skills so often referred to in the literature (Semel and Rosner, 2003).

In the narrative elicitation task (see TABLE I), the narratives were rated as low in structure coherence, process complexity and in content diversity. Nevertheless, in this specific test, the patient showed good use of paralinguistic devices and lexically encoded devices (Evaluative Commitment: 4), with variability of themes and social enhancers (Themes: 4), allowing him to engage and maintain an audience's interest and involvement. Thus, despite several studies claiming preserved linguistic and narrative skills, we found poor performance in linguistic and narrative tasks, which implicate integrative and abstraction skills associated with a general intellectual impairment (Reilly *et al*., 2004; Gonçalves *et al*., 2004).

Also, the attention skills of this patient are impaired, as demonstrated by his performance in the Toulouse Piéron Test (at the 1st percentile), showing some difficulties and a certain incapacity to sustain attention and resist distractions. In fact, WS subjects usually have a propensity toward inattention and are easily distracted (Greer *et al*., 1997; Semel and Rosner, 2003).

The patient shows several impairments in reasoning and abstraction skills as revealed by the WISC-R subtest scores (low performance on Comprehension: 5; Arithmetic: 0; Similarities: 12; and Picture Arrangement: 1). He also shows several perseverative errors in performing the different tasks and planning difficulties

TABLE I
Narrative Elicitation Task

	Score (Likert scale 1-5)*
Narrative Structure and Coherence	
Orientation	2
Structural Sequencing	2
Evaluative Commitment	4
Integration	2
Narrative Process and Complexity	
Objectivation	2
Emotional Subjectivation	1
Cognitive Subjectivation	1
Metaforisation	1
Narrative Content and Multiplicity	
Themes	4
Events	2
Scenes	2
Characters	2

* 1 (low performance) - 5 (high performance)

(he was not able to performance Trail Making Test B), which are consistent with the reported problems in this executive functioning area. Indeed, persons with WS frequently show deficits in general tests of conceptual knowledge, problem solving tasks and number, weight and substance conservation (Bellugi *et al.*, 1994; Bellugi *et al.*, 2000).

The cognitive profile of this patient illustrates the typical cognitive features that usually are associated with this genetic syndrome. He showed deficits in visuospatial cognition, attention, conceptual knowledge and problem solving tasks but he did not display the relatively spared linguistic and narrative abilities, so often referred to in the literature.

Practical Implication

This description of the patient's cognitive functioning should allow the design of an individualised cognitive rehabilitation programme in order to optimise impaired areas of functioning. The data from the neuropsychological assessment will assist in developing a cognitive stimulation therapy, promoting neurofunctional adapted activities that focus repeatedly and in a plurimodality on the cognitive strengths and weaknesses of the patient, with the aim of improving functional and cognitive performance. Our rehabilitation programme was designed on the assumption that cognitive functioning can improve by general stimulation of the neurocognitive system and by the rehabilitation of specific cognitive functions. Specific tasks have been designed aiming at enhancing language strengths, improving discourse and narrative skills (for example, identifying, describing and arranging the essential elements of a discourse topic; specifying the events or episodes of the story, describing reactions to those events or episodes of the story, and describing the story setting), promoting verbal and visual memory, stimulating manipulative performance ability and fine motor skills, reinforcing arithmetic, reasoning and simple problem resolution (like the use of coins in daily life activities), and promoting visual perceptive system activity (displaying, for example, visual and spatial stimuli, as well as specific discrimination, description, matching and spatial orientation tasks).

It must be noted that individuals with WS display a wide range of deficits, problems, and difficulties that must be taken into account in designing therapeutic programmes and they usually respond better to a structured therapy characterised by specific learning tasks and guided learning experiences (Semel and Rosner, 2003).

Summary

Williams Syndrome (WS) is a rare neurodevelopmental disorder, approximately occurring 1 in 20 000 live births, caused by a submicroscopic deletion on band q11.22-23 in chromosome 7. Their clinical characteristics include an uneven profile, characterised by physical, developmental and neurocognitive features. They also present desadaptative behaviours, with a strong impulse to social contact. Given this uneven cognitive, behavioural and neuroanatomic profile, this paper focuses on exploring these specific features. In order to do this, we used a broad neuropsychological battery and analysed the data to design an individualized rehabilitation program, which focus was to improve weak areas of performance.

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