

Evolution of Neurologic Features in Williams Syndrome

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As a part of a large multidisciplinary clinical and research follow-up study, 47 Williams syndrome patients underwent detailed neurologic testing. Because previous studies have documented the absence of major neurologic signs in Williams syndrome, the neurologic testing focused on soft signs. Previous findings of impairment of both gross and fine motor coordination were confirmed, and the presence of mild cerebellar and extrapyramidal signs was documented. In a 4-year follow-up study, an age-related pattern was revealed: soft extrapyramidal signs became more evident from 8 years of age and increased in the 14+ age group. The results are discussed according to a hypothesis related to the dopaminergic system involvement in Williams syndrome: anomalous organization or accelerated ageing process. © 2007 by Elsevier Inc. All rights reserved.

Gagliardi C, Martelli S, Burt MD, Borgatti R. Evolution of neurologic features in Williams syndrome. *Pediatr Neurol* 2007;36:301-306.

Introduction

Williams syndrome, a rare genetic disorder affecting 1 in 20,000 births, is caused by a deletion on the long arm of chromosome 7 (band 7q11.23) [1,2]. The disorder is characterized by a multisystem involvement. The major physiologic features are typical elfin facial appearance, frequent infantile hypercalcemia, cardiovascular problems (including supraaortic stenosis and hypertension), and frequent hyperacusis [2]. The neurocognitive profile is characterized by a pattern of relative strengths in particular components of expressive language, musical abilities, and face processing but relative weaknesses in nonverbal

functions, such as spatial cognition and visual-motor abilities [3-5]. This peculiar cognitive pattern has been investigated in many recent cognitive and behavioral studies, to identify whether there are genuine dissociations between abilities that could be interpreted as evidence for spared cognitive modules. At the same time, many studies have targeted the clinical and cardiologic features of the syndrome; due to the lack of elastin, an accelerated ageing limited to facial and somatic characteristics in Williams syndrome has been documented. In their follow-up study, Cherniske et al. [6] suggested a mild accelerated ageing in Williams syndrome.

Among the clinical studies less attention has been paid to the neurologic abnormalities in Williams syndrome, though a delay in the acquisition of motor milestones, clumsiness and deficit in motor coordination are commonly referred.

Trauner et al. [7] found a greater impairment of gross and fine motor coordination, oromotor skills and cerebellar functions in Williams syndrome subjects. Chapman et al. [8] in a cross-sectional study with 24 subjects affected by Williams syndrome demonstrated that the neurologic profile in Williams syndrome varies across the life span, with muscular tone increasing with age, confirming the findings of Morris et al. [9], who described that older children develop progressive joint limitation and hypertonía.

The aim of the present work was to investigate the neurologic features of Williams syndrome and the presence or absence of neurologic soft signs in the pyramidal, cerebellar and extrapyramidal systems in a sample of 47 Williams syndrome patients followed in a large multidisciplinary study and to follow the natural history of the neurologic pattern in time to determine whether an evolution was detectable. In a first part we cross-evaluated all subjects. We then performed a developmental study with a follow-up of 4 years involving a subgroup of 27 subjects.

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Received August 7, 2006; accepted January 2, 2007.

Table 1. Proportion of patients in each age group showing signs at first examination

	Age Group, yr			All Ages (n = 47)	P Value
	3-7 (n = 18)	8-13 (n = 15)	14+ (n = 14)		
Pyramidal signs					
Brisk deep tendon reflexes	57.7%	21.4%	28.6%	42.6%	0.051
Abnormal plantar response	7.7%	0.0%	0.0%	4.3%	0.246
Cerebellar signs					
Mild dysmetria	30.8%	42.9%	14.3%	31.9%	0.963
Tremor	7.7%	0.0%	0.0%	4.3%	0.246
Braking	42.3%	78.6%	85.7%	59.6%	0.011
Hypodiadochokinesia	96.2%	100.0%	85.7%	95.7%	0.431
Ataxia, ambulation	11.5%	0.0%	0.0%	6.4%	0.151
Positive cerebellar	88.5%	100.0%	100.0%	93.6%	0.151
Extrapyramidal signs					
Choreiform movements	26.9%	64.3%	85.7%	46.8%	0.002
Dystonic movements	15.4%	78.6%	71.4%	42.6%	0.001
Involuntary movements	23.1%	64.3%	28.6%	36.2%	0.240
Facial grimaces	26.9%	92.9%	85.7%	55.3%	0.001
Rigidity	3.8%	14.3%	42.9%	12.8%	0.001
General signs					
Proximal hypotonia	96.2%	100.0%	100.0%	97.9%	0.417

Percentage of patients in each age group showing symptoms at test. The linear-by-linear association test (also called the Mantel-Haenszel statistic; $df = 1$) was used to assess whether there was a change in the proportion of patients showing symptoms in the older, as compared to younger age groups (significant values are highlighted in bold italics). With increasing age, there was a significant increase in the number of patients showing signs of braking, choreiform movements, dystonic movements, facial grimaces, and rigidity.

Materials and Methods

After informed consent was obtained, we selected a sample of 47 patients from the Williams syndrome population followed up in our Institute. The subjects were selected with the exclusion criteria of a history of delivery problems, previous pathology that could affect the neurologic examination and age less than 3 years. The sample was thus composed of 21 females and 26 males, mean age 11.08 years (range, 3-30 years) with a typical deletion (7q11.23) confirmed by cytogenetic fluorescence in situ hybridization analysis. Three patients were undergoing antihypertensive therapy but none of the sample were on antipsychotic drugs. The neurologic examination was part an annual follow-up assessment which formed a section of each patient's yearly medical check.

No control group was included as far as all the examinations were standardized ones.

A complete neurologic examination was performed using a standard neurologic examination form with a more exhaustive examination in order to detect soft signs by means of drift and rapid hand movements, modified by Touwen [10]. In particular we examined responses related to the cranial nerves, motor and sensory functions, tone, strength and gait. Involuntary movements were defined as present or absent, and identified as involuntary if not targeted, abrupt movements of hands or arms (or other districts) were detectable during the time of the observation; dystonic and choreoathetotic movements of hands or fingers were defined as present or absent and were elicited by a request to hold the arms stretched forward. Facial grimaces were defined as the presence of involuntary movements involving the facial area (involuntary and frequent movements of facial muscles, not targeted and not related to the context). No distinction was made among muscles of different facial areas.

Half of the sample was examined by one neurologist and the second half was performed by a different one; a third neurologist supervised all the examinations in order to guarantee same rating method.

The mental status examination was not considered in this study.

Study 1: Cross-sectional Study

All of the 47 Williams syndrome patients underwent the neurologic examination, performed as described above. For the analysis of results,

first we examined the performance of the whole sample, then divided the sample into three age groups: less than 7 years (18 subjects), between 8 and 13 years (15 subjects), and older than 14 (14 subjects) and analyzed the data group by group (Table 1).

Study 2: Developmental Study

After 4 years, a subgroup of 27 (14 male, 13 female) participants from study 1 was followed up with a second set of neurologic examination. The second set of examinations was performed with the same criteria as the first and the symptoms were clustered as in the cross-sectional study. Mean chronological age and the number of participants in each age group are given in Table 2.

Analysis

The neurologic evaluation was designed to assess specific motor and sensory neurologic functions. Individual items were combined into related clusters, including pyramidal, cerebellar and extrapyramidal signs. In particular for the pyramidal signs the clusters combined the presence/absence of hyperreflexia or deep tendon reflex abnormalities and abnormal plantar response. The cerebellar signs considered for the clusters were the presence/absence of: mild dysmetria, tremor, braking, hypodiadochokinesia, ataxia of walking (gait), and difficulty of balance indicated by cerebellar sensitization tasks (tandem gait). The extrapyramidal signs for the clusters were the presence/absence of: choreoathetotic, dystonic and involuntary movements, indicated by sensitization task, facial grimaces and limb rigidity (increased tone).

Statistical analyses were performed using the Mantel-Haenszel statistic (also called the linear-by-linear association statistic). Values of $P < 0.05$ were considered as statistically significant.

The correlational analysis of the cross-sectional study was completed using the McNemar test.

Table 2. Proportion of patients in each age group who showed neurologic signs at first and second examinations

	Age Group 1 (n = 7)		Age Group 2 (n = 13)		Age Group 3 (n = 7)		All Patients (n = 27)	
	First	Second	First	Second	First	Second	First	Second
Age at examination	5.17 yr	9 yr	10.03 yr	14.13 yr	20.06 yr	24.51 yr	11.51 yr	15.49 yr
Pyramidal signs								
Brisk deep tendon reflexes	71.4%	71.4%	30.8%	30.8%	28.6%	28.6%	40.7%	40.7%
Abnormal plantar response	14.3%	14.3%	7.7%	7.7%	0.0%	0.0%	7.4%	7.4%
TOTAL	42.9%	42.9%	19.2%	19.2%	14.3%	14.3%	24.1%	24.1%
Cerebellar signs								
Mild dysmetria	28.6%	42.9%	30.8%	30.8%	42.9%	42.9%	33.3%	37.0%
Tremor	0.0%	0.0%	0.0%	0.0%	14.3%	14.3%	3.7%	3.7%
Braking	28.6%	28.6%	69.2%	69.2%	100.0%	100.0%	66.7%	66.7%
Hypodiadochokinesia	100.0%	100.0%	92.3%	92.3%	100.0%	100.0%	96.3%	96.3%
Ataxia, ambulation	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Positive cerebellar	85.7%	85.7%	100.0%	100.0%	100.0%	100.0%	96.3%	96.3%
TOTAL	40.5%	42.9%	48.7%	48.7%	59.5%	59.5%	49.4%	50.0%
Extrapyramidal signs								
Choreiform movements	14.3%	14.3%	76.9%	84.6%	57.1%	71.4%	55.6%	63.0%
Dystonic movements	14.3%	42.9%	69.2%	76.9%	85.7%	100.0%	59.3%	74.1%
Involuntary movements	28.6%	42.9%	61.5%	76.9%	28.6%	42.9%	44.4%	59.3%
Facial grimaces	0.0%	0.0%	61.5%	69.2%	71.4%	71.4%	48.2%	51.9%
Rigidity	0.0%	0.0%	30.8%	30.8%	28.6%	28.6%	22.2%	22.2%
TOTAL	11.4%	20.0%	60.0%	67.7%	54.3%	62.9%	45.9%	54.1%
General signs								
Proximal hypotonia	100.0%	100.0%	92.3%	92.3%	100.0%	85.7%	96.3%	92.6%

Results

All the patients showed some degree of neurologic deficit identified with the neurologic assessment, but with no major neurologic symptoms.

Study 1: Cross-sectional Study

Cranial nerve abnormalities were absent; strength was within normal limits. Tone abnormalities were frequent: proximal hypotonia was present in all but one (97.9%) patient; mild rigidity was present in six patients (12.8%). No abnormalities of sensation were found.

Abnormalities of deep tendon reflexes consisting of brisk deep tendon reflexes were present in 20 patients (42.6%). Abnormal plantar response was present in two patients (4.3%). Some soft cerebellar signs were more frequent: mild dysmetria (31.9%), hypodiadochokinesia (95.7%), difficulties in balance as shown by cerebellar sensitization tasks (tandem gait) (93.6%), braking (59.6%); ataxia in walking was rare (6.4%). No major extrapyramidal signs were evident; soft signs due to extrapyramidal system and elicited by sensitization had different distribution: choreiform movements were evident in 22 subjects (46.8%), dystonic movements in 20 (42.6%), involuntary movements in 17 (36.2%), facial grimaces in 26 (55.3%) (Table 1).

As can be seen from Table 1, the pattern of neurologic symptoms differed across the age range. In general, symptoms related to the cerebellar system, and though quite common they showed no consistent change with participant age group, although braking significantly increased and other symptoms were reported in a very high

or a very low proportion of participants. Soft extrapyramidal signs tended to increase with a significant rise in all symptoms examined except for involuntary movements. For involuntary movements there was a decrease in the oldest patient group in comparison to the intermediate group (age 8-13).

The relationships between age group and neurologic features in Table 1 does not seem to be due to participant sex or antihypertensive drug therapy as there was no linear-by-linear association between age group and sex ($P = 0.104$) and/or between age group and antihypertensive drug prescription ($P = 0.527$).

Study 2: Developmental Study

The developmental development symptoms of Williams syndrome over 4 years is presented in Table 2.

As can be seen from the table the percentage of individuals with many of the symptoms does not change during this 4-year period. In study 1 there was no consistent pattern of increase in symptoms related to the cerebellar system but there was generally an increase in soft extrapyramidal signs. Taking the three age groups together and comparing the frequency of the different pyramidal, cerebellar and extrapyramidal signs, a similar pattern was found in the developmental data. Between the first and second examinations there was no significant change in the frequency of symptoms related to the cerebellar system (Wilcoxon signed rank test, $Z = 0.58$, $n = 27$, $P = 0.56$), but there was a significant increase in soft extrapyramidal signs ($Z = 2.64$, $n = 27$, $P < 0.01$). Looking in more detail at the different extrapyramidal signs (Table 2) it can

be seen that the increase in both dystonic and involuntary movements is particularly marked: in every age group a increase in the incidence of these two extrapyramidal signs is recoded.

Discussion

We conducted a cross-sectional study of the neurologic conditions in Williams syndrome. As hypothesized and in agreement with the data in literature, no major neurologic signs were found; on the contrary, many mild signs were detected, involving mainly cerebellar functions and the extrapyramidal system. These data suggest the existence of complex mild neurologic dysfunctions in all Williams syndrome cases and in different ages. With the present study, we have attempted to classify these minor neurologic dysfunctions more clearly and followed them with increasing of age.

The neurologic profile of Williams syndrome is peculiar and varies with age, as previously reported [7,8]. The distribution of signs in our population is different according to age: mild cerebellar signs were frequent in the present sample from childhood up to adulthood, even if the proportion in incidence of every single cerebellar sign is differently distributed in the three different age groups. However, the number of mild extrapyramidal signs increases significantly with age. For example, rigidity is absent in the youngest subjects, is very scarce until 13, and tends to increase afterwards.

A similar pattern was previously reported by Chapman et al. [8], in a study documenting abnormalities in motor coordination, tone, and gait in 24 Williams syndrome children aged from 2 up to 30 years. The study found that tone abnormalities varied as a function of age, with decreased tone prevailing in younger subjects and increased tone in older ones. Gait and coordination abnormalities were documented in all subjects, indicating that these abnormalities could not have been simply problems related to the degree of maturity. Chapman et al. [8] did not find changes in cerebellar functions in Williams syndrome and noted that increasing tone with age is not uncommon in cerebral palsy.

In another study, Trauner et al. [7] compared a small group of eight Williams syndrome patients (mean age 16.7) with six subjects with Down syndrome, concluding that the presence of gross and fine coordination, oromotor skills, and cerebellar functions are more impaired in Williams syndrome subjects, compared with Down syndrome patients, perhaps due to the existence of as yet undefined metabolic deficits in Williams syndrome.

We could not find any previous study investigating mild extrapyramidal signs in Williams syndrome. The finding of an age-related increase in mild extrapyramidal signs leads us to hypothesize that increased tone could be part of a soft extrapyramidal pattern that becomes increasingly evident as individuals with Williams syndrome mature. We found no correlation with clinical signs or hyperten-

sion; subjects fit the initial criteria and no significant event (cardiological or clinical) took place in the 4-year interval between the two examinations.

The neurologic pattern in our Williams syndrome sample is complex: a mild involvement of different systems is documented, with a part of clustered signs remaining similar along with age. Cerebellar signs are more frequent than pyramidal ones, and tend to remain unchanged; extrapyramidal signs become more evident, suggesting in some way an evolution or progression in time, although not in all of the subjects. The oldest patient was 30; we have no data about the neurologic pattern in older patients. Up to now, we cannot identify any peculiarity in the Williams syndrome subjects who are prone to develop extrapyramidal signs distinguishing them from the others (the minority of our sample) who are not. The clinical extrapyramidal signs evoke a lack of control and a postural dysfunction, as shown by a significant increase in the incidence of dystonic and involuntary movements.

We can offer no final explanation for our findings, but some hypotheses can be made.

1. Individuals with congenital syndromes tend to have more complex deliveries than healthy subjects. Although these complications are often seen as clinically insignificant, it is possible that they could result in the rare presence of pyramidal signs. Although there is no strong support for this explanation in our data, the fixed nature of pyramidal signs may indicate that the underlying neural problem is set early in development.
2. The presence of cerebellar signs in Williams syndrome is important, in that these are very common in the sample. The cerebellar signs are characterized as soft, without any real ataxia but with impaired control of balance. These findings match not only the typical report by families of clumsiness and a tendency to fall becoming less evident as children with Williams syndrome grow up, but also fit with reports by many parents that complex tasks requiring fine motor control are often very difficult for their Williams syndrome children. The learning of many skilled tasks (e.g., to cycle) is hard and slow for the majority of Williams syndrome patients; this impairment is linked to the complex neuroanatomical and neurophysiological pattern involved in these complex tasks. Outside the literature on Williams syndrome, the involvement of cerebellar structure in the type of complex sequential tasks with which Williams syndrome individuals have problems is well documented. It may therefore be no surprise to many researchers that we found soft cerebellar impairments in individuals with Williams syndrome during neurologic examination. Compensatory strategies allow individuals with Williams syndrome to improve in coordination and motor skill as they get older, despite the persistence of cerebellar signs. Jones et al. [11] documented a disproportionate enlargement of the cerebellum that was stable across different age

groups in Williams syndrome. They also tried to suggest which cognitive domains among the more stable ones during development in Williams syndrome (face recognition, visual spatial, social abilities) could be related to cerebellar functions. Neural imaging studies also reported the presence of impairment in cognitive functions and related them to the cerebellum in Williams syndrome [12,13].

3. The involvement of extrapyramidal system in determining the Williams syndrome phenotype has been discussed in studies on the cognitive profile: basal ganglia and the cerebellum play an important role in motor skill learning, the former being responsible for the correct sequence of motor acts and the latter of their temporal sequencing [14]. Many studies have documented an enlarged cerebellum and, in particular, an expansion of the neocerebellar areas [4,5,11,15-17]. In studies comparing Williams syndrome individuals with typically developing control subjects or subjects with Down syndrome, brainstem structures, the caudate nuclei, and basal ganglia (included lenticular nuclei) were found to have reduced volume [4,5,16,18]. These last findings are particularly interesting with regard to the mild extrapyramidal signs in Williams syndrome documented here and their tendency to increase with age.

The impairment of the extrapyramidal system suggested by our data may be speculatively linked to a dysfunction in the nigrostriatal dopaminergic system. It may be hypothesized that the abnormal development suggested by Thompson et al. [19] could also imply an anomalous trajectory that involves the cortical-subcortical circuits as well as the thickening in the temporal cortex.

The unexpected increased frequency of mild extrapyramidal signs with age found in the present studies could suggest another, though not contradictory, hypothesis: that the increased frequency is a result of the early onset of the ageing process in individuals with Williams syndrome. In the normal ageing process, there is a progressive increase in deregulation of the nigrostriatal system resulting in mild extrapyramidal signs in old age [20-22]. Other authors believe that extrapyramidal signs are due to neurodegenerative syndromes associated to ageing [23] or are predictors of dementia [24]. Individuals with Williams syndrome show accelerated ageing of the facial and somatic characteristics due to lack of elastin [9]. However, accelerated ageing is not limited to the face: Cherniske et al. [6] found evidence of mild accelerated ageing in Williams syndrome with early onset of cataracts, high-frequency sensorineural hearing loss, gastrointestinal problems including diverticulosis, altered glucose tolerance, and decreased bone mineral density.

Lesions or diseases involving basal ganglia have been found to cause movement disorders that can be understood as a failure to facilitate desired movements or a failure to inhibit unwanted movements or both. The disturbance

found in Williams syndrome could be due to a failure in inhibition of involuntary movements and mild dystonia. There is mounting evidence that some dystonias are associated with relative dopamine deficiency or dopamine type 2 receptor dysfunction [14,25].

An intriguing connection comes from studies on children with neurodevelopmental disorders, and in particular with mild motor problems detected in the developmental coordination disorders, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV [26]: in development coordination disorders, specific deficits in sensory motor integration, impaired motor functions and motor planning [27], or dysfunctions in the perceptive system [28,29] have been hypothesized. When attention deficit is an associated factor, a diagnosis of deficits in attention, motor control, and perception is made on the basis of the classification proposed by Gillberg et al. [30,31]. Motor impairment in attention deficit disorder has been related to disturbed executive functions in which the processing of sensory information could be affected [32] and deficient dopaminergic frontostriatal pathways have been suggested as a possible background [33].

Some authors [34,35] have suggested similarities between Williams syndrome and attention deficit disorder, mainly from a behavioral and cognitive point of view, given the deficit of attention and the hyperactivity common in Williams syndrome. As hypothesized in attention deficit disorder, an impairment of dopaminergic pathways could be involved in Williams syndrome. Moreover, among the different genes investigated for attention deficit disorder, in linkage studies, a key role for SNAP-25 (synaptosomal associated protein 25) has been claimed [36]. The priming step of synaptic vesicle exocytosis is thought to require the formation of the SNARE complex, comprising synaptobrevin, SNAP25, and syntaxin [37], which is deleted in the typical Williams syndrome deletion. The modulation of binding and uptake of neurotransmitters, namely of dopamine, could be crucial also in Williams syndrome, and need future and large investigations.

Apart from the etiopathogenetic hypothesis, the present study has documented the existence of a pattern of mild neurologic signs that could explain in generic terms the clumsiness that has been used quite often to describe the characteristics of the voluntary movement and gait in Williams syndrome; this pattern, involving different cerebral pathways, tends to change in time only as regards the extrapyramidal signs. This could lead to a different approach to movement control in Williams syndrome and extend the data on the natural history of the disorder.

The authors are grateful to the patients and their families for their kind cooperation. The authors would like to thank Lucia Atzeni, Laura Cesena, and Paolo De Grate for their help in the collection of the data.

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