Williams Syndrome: Pediatric, Neurologic, and Cognitive Development

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This study examines the developmental history of 32 Williams syndrome patients, positive to the fluorescence in situ hybridization (FISH) test. The information is intended to provide help for early diagnosis and appropriate stimulation of these patients. In the sample reported here, only about half of the patients referred with presumptive diagnosis were in fact FISH+, indicating that facial dysmorphism may not be the most reliable sign for diagnosis. Initial pediatric signs are developmental delay and nocturnal irritability. In consultation, facial dysmorphies and heart murmur are detected. There is also low birth weight, failure to thrive, unsuccessful breastfeeding, and gastroesophageal reflux. All these symptoms are strongly suggestive of Williams syndrome. Subsequent steps consist of cardiologic studies. Our results indicate that the triad of symptoms consisting of infantile hypercalcemia, dysmorphic facies, and supravalvular aortic stenosis, which until recently was considered fundamental for Williams syndrome diagnosis, is not usually present and does not lead to an early diagnosis. Cognitively, these children are characterized by hypersociability, hyperacusia, deficient visuoconstructive abilities, attentional deficit and hyperactivity, and in some cases, spontaneous musical interests. There are no special verbal skills. The results of this study indicate that the concept of Williams syndrome patients as language- and musically-gifted is not fully accurate.

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Introduction

Williams syndrome is a genetic disease caused by the hemizygous deletion of a segment in chromosome 7q11.23, which includes about 25 genes. This defect is not observed in standard karyotypes and requires a clinically directed, molecular genetic analysis for its detection [1-6]. Williams syndrome includes several phenotypic features which affect most organic systems and include congenital heart disease, mental retardation, and a characteristic facies [7-11]. Despite this, diagnosis of Williams syndrome can be delayed for years, especially in those cases in which the most common cardiopathy, supravalvular aortic stenosis, is not present [12]. Williams syndrome patients also manifest a peculiar cognitive profile which has been often described as consisting of outstanding social, verbal, and musical skills combined with poor performance in visuoconstructive tests [13-20]. For these reasons, in the last decade Williams syndrome has been the subject of intense investigations in the study of gene–cognition correlations. Although research in this line has been of the highest interest, there is a noticeable contrast between the specialized molecular-cognitive-behavioral knowledge of these patients and the situation of their parents who have to deal with them daily, or the knowledge that many health professionals have about this syndrome. In this context, this report describes the most outstanding clinical characteristics observed in our experience of 32 cases including infants, children, and adolescent patients. This information was acquired after a scheduled interview with parents and physical and neurologic examinations of the patients; also included were data on developmental milestones. This data will be useful for an earlier diagnosis and therapeutical intervention, for a more documented and effective familial support, and also

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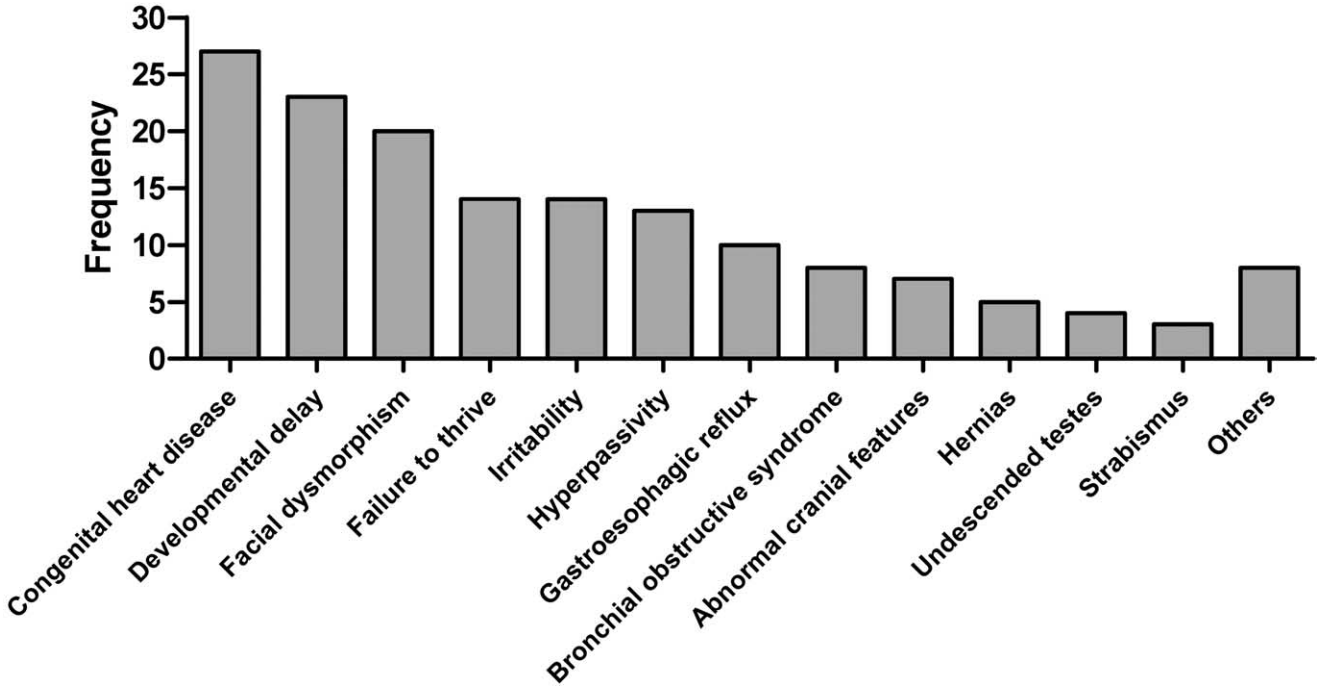

Figure 1. Complaint at first appointment of 32 Williams syndrome patients.

for a wider knowledge of the natural history of this disease.

Patients and Methods

Patients

Between June 2000 and May 2002, 101 children with presumptive diagnosis of Williams syndrome were directed by diverse health specialists to the Genetics Unit of Hospital Clínico Universidad de Chile. These patients were subjected to a fluorescence in situ hybridization (FISH) test with a Vysis probe complementary to the chromosome band 7q11.23, which includes the genes for elastin (ELN) and other neighboring genes (RFC2, WSCR1, FZD3, STX1A, and LIMK1). This test is a standard diagnostic method and does not allow one to distinguish between different types of mutations leading to Williams syndrome. Williams syndrome diagnosis with the deletion was confirmed in 49 subjects. From this sample, we report here the results of 32 cases in which a complete clinical assessment was performed. At the time of FISH confirmation, 6.25% of the patients were between 1 and 23 months of age; 37.5% were between 2 years to 5 years and 6 months; 40.6% between 6 years and 13 years and 11 months; and 15.6% were between 14 years and 15 years and 11 months. The subjects were 56.25% male and 43.75% female.

Methods

FISH+ patients and their relatives were notified about the research and consented to participate in it. Patients were physically examined by a geneticist and a neuropediatrician; their parents were interviewed, according to a preestablished schedule, concerning the perinatal period, reason of the first clinical appointment, morbidity, development, outstanding behavioral characteristics, and familial background.

Results

Motive of First Appointment and Presumptive Diagnosis

The first signs and symptoms were usually evident in infants and were the motive for clinical consultation, but did not always lead to early diagnosis of Williams syndrome (Fig 1). The focus in this study was on early detected signs whose proportion may not reflect the incidence observed at later ages; for example, at first appointment facial dysmorphism appears with a lower incidence than in the school age population. Congenital heart disease (84.3% of the cases) was usually established after detection of a heart murmur in the routine pediatric examination. Detection of Williams syndrome tended to be earlier when supravalvular aortic stenosis was confirmed. In patients with supravalvular aortic stenosis, age at diagnosis of Williams syndrome was $1.45 + 0.28$ years, whereas in patients without supravalvular aortic stenosis (even though having other heart diseases) it was 4.94 ± 1.69 years ($P = 0.0275$). Developmental delay was the second cause of early consultation (71.9%), which could be global (18/23 cases), purely motor delay (4/23 cases), or isolated language delay (1/23 patient). Dysmorphic facies were detected early in 62.5% of the cases. However, this characteristic was usually not obvious to the parents and was detected by health professionals (18/20 cases), and in 3/20 cases was observed at birth as nonspecific alterations that did not lead to a diagnosis of Williams syndrome.

Irritability (59.4% of the patients) was described as sleep disturbances, frequent and uncontrolled crying and was interpreted as a sleeping disorder or cramps. In one case irritability was correlated with transient hyperammonemia. On the other hand, hyperpassivity, i.e., excessively quiet behavior and minimal or no crying, was observed in 40.6% of the cases. In three of these cases, there was diurnal hyperpassivity and nocturnal irritability. Failure to thrive was another cause of early consultation (43.7%), as well as gastroesophageal reflux and vomiting (31.2%). In 25% of the cases, the study leading to Williams syndrome diagnosis was initiated after repeated episodes of bronchial obstructive syndrome. In other cases, patients presented with abnormal cranial features (21.9%, including one case of congenital microcephaly and two of plagiocephaly, one of which required craniopasty), inguinal hernia (15.6%), undescended testes (12.5%), and strabismus (9.4%). In isolated cases (3.1%), first time medical attention was motivated by hyperactivity, non-delivery associated peripheral facial palsy, posterior cleft palate, precocious dentition, congenital hip dysplasia, clubfoot, episodes of cyanosis (attributed later to heart disease), and hemangioma.

In our sample, a trend to decrease the age of the presumptive clinical diagnosis of Williams syndrome was observed, which in most cases resulted from multidisciplinary discussion and occurred after a series of consultations with different specialists. On average, the two infants were diagnosed at 2.4 months whereas the five adolescents were diagnosed at 9.2 ± 7.05 years of age.

Perinatal History

The main data obtained from interviews with parents were validated by registered information. Parents were relatively young; average maternal age was 27.2 ± 5.8 years; paternal age was 29.6 ± 4.6. Gestation was nearly normal (38.6 ± 3.2 weeks). Birth weight was low (2.77 ± 0.5 kg); height at birth was low (47.2 ± 2.6 cm); Apgar score was close to optimal (mode at first and fifth minutes was 9). Pregnancy pathologies were intrauterine dwarfism (12.5%), urinary infection (12,5 %), miscarriage symptoms (9.4%), gestational diabetes (9.4%), gravid hyperemesis (6.3%), placenta previa (6.3%), and toxemia of pregnancy (6.3%). Exposure to substances was low (antibiotics 4 cases, domperidone 3 cases, tobacco 1 case, hormonal contraceptives 1 case). Delivery was vaginal in 17 cases (one of them with forceps). Fifteen cesarean sections were programmed by delayed intrauterine growth and signs of premature delivery. Neonatal jaundice was considered idiopathic in 25% of the cases; in three cases it occurred in the context of neonatal hepatitis. Neonatal hospitalizations were for phototherapy, for weight increase, and to treat cyanotic episodes (related to cardiopathy which was detected later). In no case was mechanical ventilation required. A diagnosis of Williams syndrome was never considered in this context, even if in some cases polymalformations were observed (heart murmur, facial and genitourinary malformations, among others). The duration of breastfeeding was exceptionally low, with an average of 4.92 ± 2.78 months and mode of 2 months, and this was always due to deficient suction. Breastfeeding lasted more than 7 months only in five cases.

Morbidity

Tables 1 and 2 present the most important instances of morbidity. These findings agree with evidence reported elsewhere [7-9,11]. The most common congenital heart disease was supravalvular aortic stenosis, which in only five cases (29.4%) required surgery. Dental pathologies included multiple cavities, microdontia, multiple diastemas, and occlusion defects. Skeletal pathology consisted of radiocubital sinostosis, clubfoot, congenital hip dysplasia, and vertebral column anomalies (the latter appeared more often during adolescence). One of the adolescent patients underwent surgery for kyphoscoliosis, with good results. Respiratory pathology was due to obstructive bronchial syndrome and repeated bronchopneumonia. Gastrointestinal morbidity consisted mainly of gastroesophageal reflux in infants and preschool children, which tended to disappear in later age, and chronic constipation, which persists in adolescence. In one case chylous diarrhea was observed. Genitourinary pathology included cryptorchidism, single testicle, enuresis, repeated urinary infections, one case of renal agenesis, and one case of duplicated pyelocalicial system. Strabismus and refractive errors were the elements of ocular pathology, plus a case of congenital palpebral ptosis. Hernias were inguinal and bilateral in most cases. Craniofacial defects included plagiocephaly, brachiocephaly, microcephaly, and one case of posterior palatal cleft. Endocrine defects were precocious puberty and one case of hypothyroidism. There were also cases of tonsil hypertrophy.

Table 1. Observed morbidity in 32 Williams syndrome patients

Morbidity	%*
Cardiovascular	85 (80)
Mental retardation	87 (75)
Dental	75 (95)
Neurologic	62 (70)
Respiratory	59
Gastrointestinal	59 (70)
Skeletal	41 (20-50)
Ocular	38
Hernias	38 (40-50)
Craniofacial	35
Genitourinary	28 (5-50)
Endocrine	8 (5-30)

* In parenthesis, data from the American Academy of Pediatrics, Committee on Genetics: Health care supervision for children with Williams syndrome (2001).

Table 2. Cardiovascular pathology found in Williams syndrome patients

Defect	Frequency
Supravalvular aortic stenosis	17
Pulmonary stenosis	7
Functional murmur*	4
Ventricular septal defect	4
Coarctation of the aorta	2
Systemic hypertension	1
Pulmonary hypertension	1
Ductus	1
Combined valvulopathy†	9

Abbreviations:
CoAo = Coarctation of the aorta
PS = Pulmonary stenosis
SVAS = Supravalvular aortic stenosis
VSD = Ventricular septal defect
* Functional murmur refers to a transient condition without clear etiology, at least for parents (it cannot be excluded that some of these are SVAS+ or PS+).
† SVAS + PS (4 cases), SVAS + VSD (2 cases), SVAS + CoAo (1 case), and PS + VSD (2 cases).

Psychomotor Development

In most aspects psychomotor development was delayed when compared with normal data [21]. Achievement curves have a lower slope, and the 100% takes longer to achieve than in normal children (Fig 2). Noteworthy, cumulative frequency graphs indicate that achievement in the production of at least five meaningful words was also much slower than observed for normative data.

Cognitive Aspects According to Clinical History

The following are some behavioral and cognitive features of children and adolescent Williams syndrome patients which are of concern to parents and health specialists, and are of relevance when considering a presumptive Williams syndrome diagnosis.

Language was reported as outstanding in only 31% of the cases, including two patients who, according to their parents, speak much but in an unintelligible jargon. However, in all cases there is a global delay of language development, with patients producing the first words at around 3 years and being semantically, morphosyntactically, and phonologically deficient until adolescence. In summary, in schoolchildren and adolescent (but not younger) Williams syndrome patients, there is a relatively preserved language in relation to general intelligence, but in no case is there outstanding linguistic ability. Nevertheless, an outstanding communicative intention and high emotional content are obvious in all of them, except for the

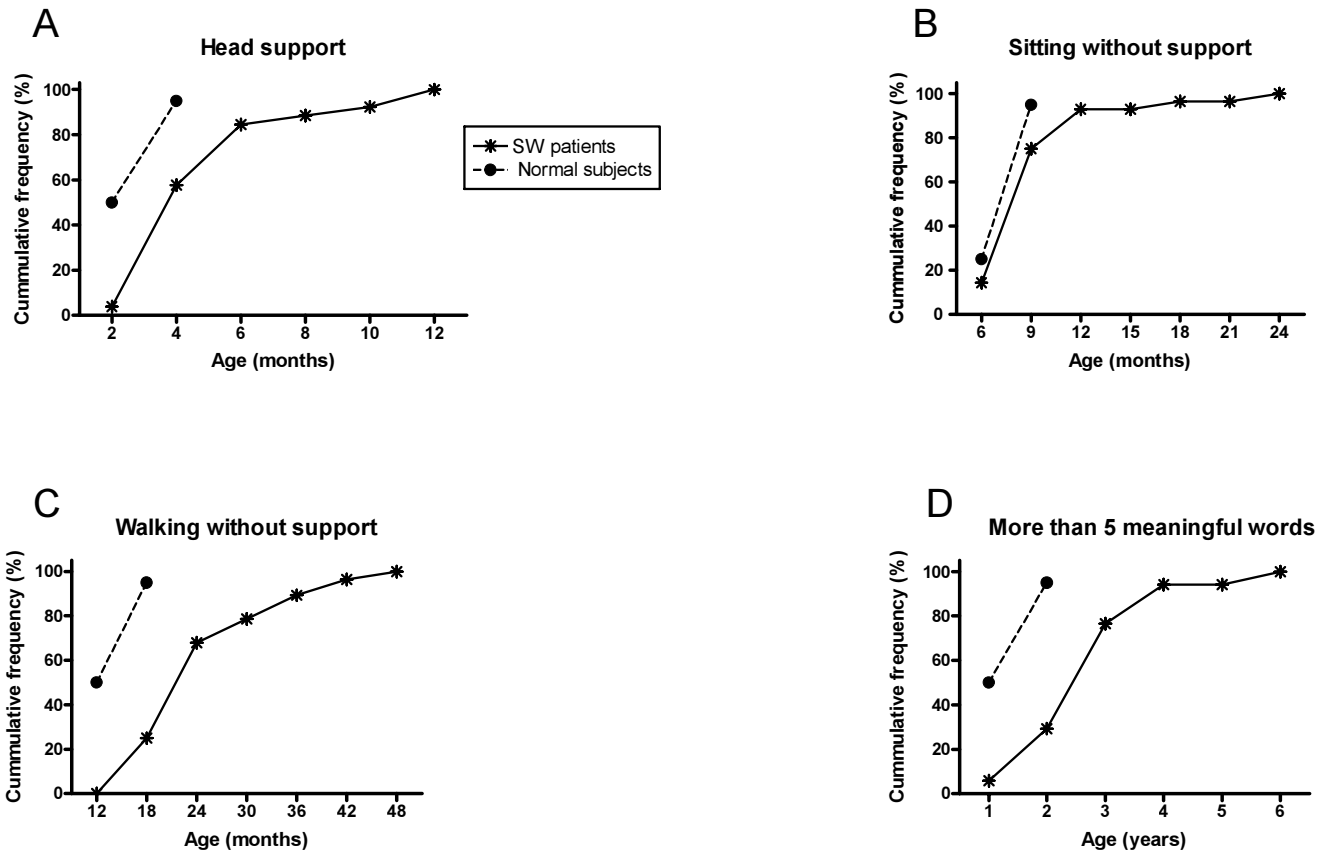

Figure 2. (A-C) Achievement of gross motor developmental milestones in 28 children with Williams syndrome. (D) Age to achieve more than five meaningful words in 17 children with Williams syndrome.

three cases with autistic features, all of whom were included in our sample.

Sociability is the most noticeable behavioral characteristic of these patients, and is spontaneously referred to in 87.5% of the cases, including one of the two infants of the sample. In preschool stages there is absolute lack of fear of strangers and no separation anxiety; there is a higher tendency to relate with adults than with children of the same age. They maintain strong eye contact, often use the words "please" and "thank you", are highly affectionate in their interactions, and are sensitive to the feelings of others.

Musical interests were reported spontaneously by parents in 81.3% of the cases (including patients with autistic features), and were evident in school ages. Parents highlight musical memory and recognition. Patients can be selective regarding the kinds of music they like. Although in some cases an ability to play musical instruments was reported, in our sample there was no case of systematic musical training. In 84.4% of the cases, parents reported hyperacusis, which produced great discomfort and was selective to certain types of sound. In five cases, parents reported an affinity for metallic sounds made with tools (such as a hammer or a saw).

Deficient visuoconstructive abilities were reported spontaneously in 37.5% of the cases, but after direct questioning the proportion increased. Patients were unable to copy drawings and manifested a dislike for the use of pencils, painting materials, and puzzles. They also had great difficulty with reading and writing. Face perception was reported to be good; they recognize people they have seen only for a few minutes or a long time ago.

Attentional deficit and hyperactivity is a salient characteristic, reported by parents and confirmed by health specialists according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria in 62.5% of the cases. This feature is common in preschool and early school age (66%), and declines in adolescence (20%). It is usually treated with stimulants, with good response. In 70% of the preschool children there was pathologic oppositionism, associated with pathologic hyperactivity (exceeding the normal hyperactive behavior of this age). Signs of anxiety were reported in 59.4% of the cases, and simple phobias in 50%. Most phobias were related to intense sounds. Obsessive behavior was observed in 46.9% of the cases.

Neuropsychiatric Evaluation

Besides retarded psychomotor development, subnormal intelligence ranged from borderline to moderate (in 100% of the cases); hyperactive behavior was observed in 68.8% (more common among preschool [67%] and schoolchildren [76.9%]), and there were three cases with autistic features. There were several other neurologic signs, summarized in Table 3. Single cases of Chiari I malformation (magnetic resonance imaging) and bilateral pallidal calcification (computed axial tomography) were also detected; both patients were female adolescents without any correlated symptoms.

Table 3. Neurologic signs found in our Williams syndrome sample

Defect	Frequency
Sensorimotor incoordination	13 (40.6%)
Hypotonia	15 (46.9%)
Joint laxity	18 (56.25%)
Hyperactive tendon reflexes	20 (62.5%)
Clumsiness of gait	20 (62.5%)
Microcephaly	6 (18.75%)

Discussion

In 2 years, we have collected a sample of 32 children and adolescents with Williams syndrome, which comprises the first large-scale study of this syndrome in Chile. Only about half of the patients who were referred to us with a presumptive Williams syndrome diagnosis were confirmed as FISH+. The high proportion of FISH– cases may have been due to the fact that a presumptive diagnosis was made by specialists who were not fully acquainted with Williams syndrome. In fact, according to our clinical evaluation, only three of the FISH– patients had a phenotype suggestive of Williams syndrome. Samples of these three patients were sent to another laboratory for further analyses. Another possible explanation for this is that facial dysmorphism is usually considered an important sign, although it can be equivocal. In a previous study [22], we observed that the most reliable morphologic features were periorbital fullness, long and smooth philtrum, and congenital heart disease (especially supravalvular aortic stenosis), while the less reliable features were anteverted nostrils, large mouth, and long and slender neck. Despite our significant experience with Williams syndrome patients, in some cases it is still difficult to make an accurate diagnosis based exclusively on facial dysmorphism (Fig 3). Nonetheless, in the last years we have detected that presumptive Williams syndrome diagnosis is made at a progressively earlier age. This fact, together with the availability of molecular diagnosis, is especially relevant when considering strategies of early stimulation.

Our morbidity and perinatal findings are close to those reported elsewhere. However, clinically we observed a higher incidence of mental retardation than in other studies (87% vs 75%, respectively). This difference becomes even higher when performing a formal intelligence quotient evaluation. In the present sample, 13 randomly selected patients were assessed psychometrically with the Wechsler intelligence scales. There was one borderline case, eight cases with mild mental retardation, and four cases with moderate retardation (adding up to a 92% incidence of mental retardation). More extended studies are needed to verify this apparent discrepancy. Patients tended to

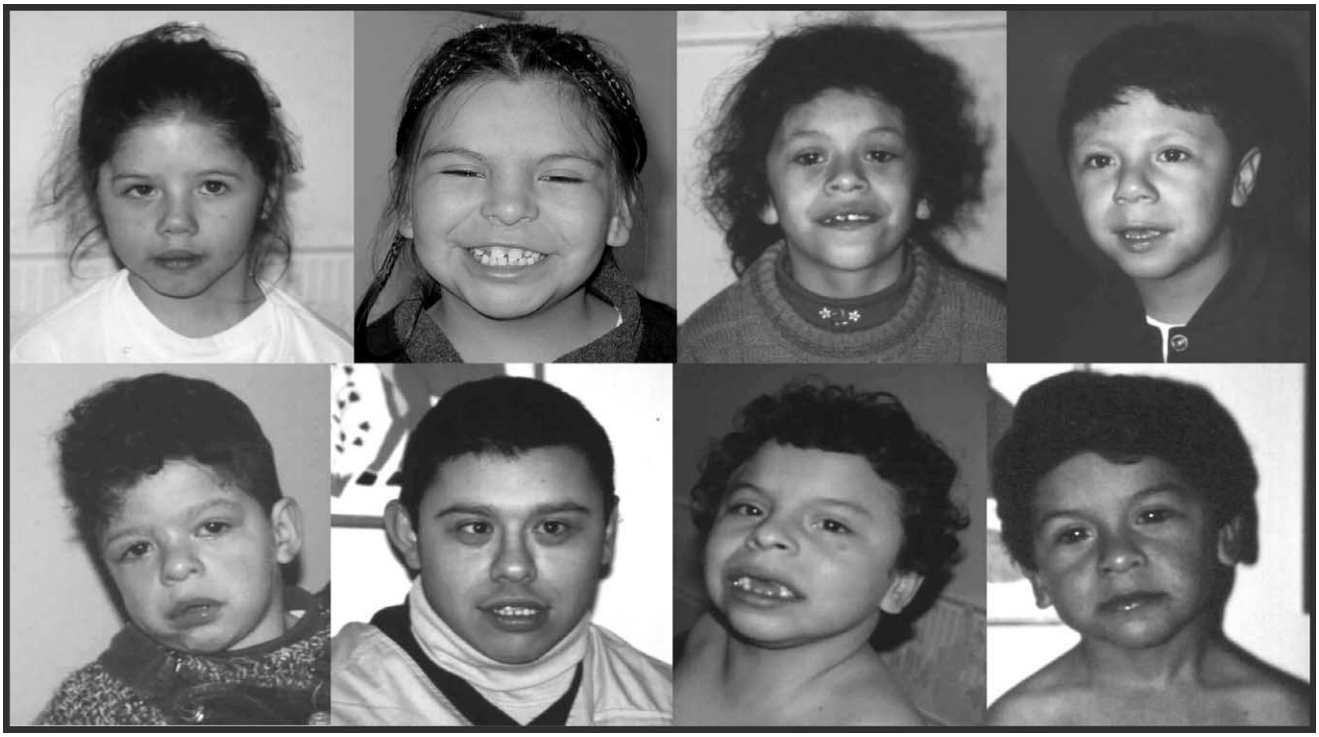

Figure 3. Faces of Williams syndrome, FISH+ patients. Note that there is some phenotypic heterogeneity, which makes clinical diagnosis difficult on the basis of facial features. In these patients, many of the facial features that have been usually described in Williams syndrome are present: anteverted nares, smooth and long philtrum, fullness of periorbital region, full cheeks, open mouth appearance. However, despite the presence of these aspects, global appearance is not always suggestive of the typical elfin face described for Williams syndrome.

perform better in the verbal than in the nonverbal part, but there were only two cases in which verbal scores exceeded the manual scores by more than 15 points. Although the dysharmony between the verbal and nonverbal scores is considered an indication of organic brain damage, in these patients it may be related to the impairment in visuoconstructive tasks. Considering that the Wechsler scale is sensitive to cultural factors, one possibility is that the discrepancy in the incidence of mental retardation between our findings and those in the literature may be due to insufficient stimulation of our patients. In fact, many of the patients in this study belong to low-income families and were diagnosed at a relatively late age. If this is correct, this situation would stress the importance of making a presumptive diagnosis as soon as possible, in order to intervene with appropriate stimulation from an early age.

Psychomotor development in Williams syndrome is scarcely documented in the literature. There is significant motor and linguistic developmental delay, which apparently exceeds the delay observed in a group of patients with Down syndrome that we are studying in parallel (preliminary data not shown). However, it is possible that these children with Down syndrome have been more properly stimulated from early infancy, which could explain the above differences. Contrary to many Down syndrome patients in our environment, who are diagnosed at birth, the patients in this study have not participated in early stimulation programs, which at least in Down syndrome, have been demonstrated to improve neurologic outcome [23,24]. Only three of our patients were able to read and write (two of them at 6 years and the other at 9 years of age; there was no relation between this skill and intelligence quotient). All three cases belong to middle-class families in which one of the parents underwent higher education.

Cognitively, the main features of Williams syndrome patients are high sociability, hyperacusis, musical interests (but not always), deficient visuoconstructive abilities, and attention deficit/hyperactivity. In our sample, abilities commonly cited in the literature such as music and language were not especially prominent. Moreover, language development was somehow delayed in these children, which contrasts with the good linguistic level that is achieved later. In our sample, the use of unintelligible jargon in the preschool stage was a common sign. Thus, we consider that the concept of language- and musically-gifted children is not the best descriptor of their abilities. As mentioned, these children are extremely sociable, and their eloquent speech may be more related to their communicative intentions rather than to their language skills.

There is a significant psychomotor delay in the achievement of motor milestones; furthermore, hypotony is observed especially in infants and preschool children. There is also deficient sucking which made breastfeeding especially difficult and brief in most of our subjects, in agreement with previous reports [9,11,25]. Interestingly, in one case imaging studies revealed bilateral calcification in the globus pallidus,

without clinical correlate. This case may merit further studies on calcium metabolism in these patients.

Initial pediatric consultations are usually due to developmental delay and to irritability (generally nocturnal, which sometimes alternates with diurnal passivity), which is interpreted by specialists as sleep disorder or colic. The physician then finds facial dysmorphies and heart murmur. There is also low birth weight, failure to thrive, unsuccessful lactation, and gastroesophageal reflux. According to our findings, this constellation of symptoms and signs is strongly suggestive of Williams syndrome. Subsequent steps should consist of cardiological and echocardiographic studies. Supravalvular aortic stenosis is the most common cardiopathy, followed by peripheral pulmonary stenosis. If one of these anomalies is confirmed, the patient should be referred to a geneticist and screened with FISH. Our results indicate that the triad of symptoms consisting of infantile hypercalcemia, dysmorphic facies, and supravalvular aortic stenosis, which until recently was considered fundamental for Williams syndrome diagnosis, is not usually present and does not lead to an early diagnosis. In those few cases in which calcium was measured, it was at normal levels. In one patient manifesting irritability, ammonia and calcium were measured. Whereas calcium was normal, ammonia levels were high. The finding reported here, although corresponding only to one case, suggests that in the study of infants with Williams syndrome, irritability, and normal calcium, an elevation of ammonia should be excluded as a possibility.

Finally, although there is intense research on the molecular and cognitive bases of Williams syndrome which promises to be an important frontier of future work [26-30], it is indispensable to increase and spread knowledge about the clinical history of these patients.

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