Dental aspects of systemic genetic diseases – Williams – Beuren syndrome and Cleidocranial dysplasia.

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Topic: Oral manifestations of systemic diseases – the importance of the cooperation between the dentist and the general physician

Consultant: Dr. med habil Zoltan Vajo

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ÖSSZEFOGLALÓ

A Williams-Beuren szindróma olyan genetikai betegség, melynek előfordulása 1 a 20000-50000 élveszületésből. Tünetei szupravalvuláris aorta stenosis, diszmorfiás arc, melyet "manó-arcúságnak" hívnak és mentális retardáció. Korai felismerése elengedhetetlenül fontos az egyes tünetek kezelhetősége szempontjából, a betegség prognózisa a korai felismeréssel jelentősen javítható. E fejlődési rendellenesség klinikailag heterogén, éppen ezért pusztán a klinikai képre támaszkodva nehezen diagnosztizálható. Másfelől azonban a genetikai teszt nem elég költséghatékony, így klinikai gyanú alapján minden egyes beteg vizsgálata nem kivitelezhető. Célunk olyan új klinikai szűrőeljárás kidolgozása volt, mely megfelelően érzékeny, specifikus, olcsó és könnyen használható. Cephalometriai analízisnek és fogászati értékelésnek vettettünk alá 33 genetikai teszttel is azonosított Williams-Beuren szindrómás beteget, valamint 100 hasonló korú egészséges gyermeket. A lágy szövetek cephalometriai analízise Williams-Beuren szindrómás páciensekben rámutatott arra, hogy normál SNA, SNB és ANB szögek mellett az ajkak a Ricketts-féle e-vonal előtt helyezkednek el. Ez minden WS páciens esetében megfigyelhető volt, míg a hasonló korú kontroll betegek egyikénél sem találtunk ilyet. Más eltérés a Williams-Beuren szindrómás betegek és a kontrollcsoport tagjai között nem volt megfigyelhető. Ez a kefalometriai eltérés Williams-Beuren szindrómás betegek diagnosztizálásában specifikus és kellő érzékenységű, míg más, hagyományos fogászati értékelések nem alkalmasak erre.

A tipikus cardiovascularis eltérések hiányában (szupravalvuláris aorta sztenózis, vagy pulmonális artériás sztenózis) a Williams-Beuren szindróma klinikai diagnózisa nagyon fiatal pácienseknél nagy kihívást jelent. Másik célunk, hogy a Williams szindrómás betegek posztnatális fejlődése során fellépő kardiovaszkuláris léziókat detektáljuk és ezen eredményeket leírjuk 29 Williams szindrómás beteg – átlagéletkoruk 12.8 év – kardiovaszkuláris státuszát retrospektíve tanulmányozva az életkor függvényben. A kardiovaszkuláris diagnózis az esetek többségében (72.4%-ban) változott. Érdekes, hogy a betegek 44.8%-ánál volt olyan életszakasz, amikor kardiológiai tünetek egyáltalán nem kerültek detektálásra. Mi több, a páciensek 65.5%-ánál megfigyelhető volt olyan életszakasz is, amikor semmilyen tipikus kardiovaszkuláris lézió, vagyis sem a diffúz vagy lokalizált SVAS sem a pulmonális aorta stenosis nem került felismerésre. Spontán regresszió és progresszió SVAS és pulmonális aorta stenosis esetében is gyakori volt. A vártnál magasabb arányban (41%) fordult elő a mitrális billentyű rendellenessége.

Tanulmányunk során megállapítottuk, hogy Williams-Beuren szindrómás betegeknél gyakori a kardiovaszkuláris tünetek időszakos hiánya vagy változása. Ezen erdemények

hozzájárulhatnak a diagnosztikai kritériumok pontositásához, valamint javasolt a Williams szindrómás betegek kardiovaszkuláris utánkövetése.

Avizsgált másik szisztémás genetikai megbetegedés, a cleidocranialis dysplasia (CCD) olyan genetikai kórkép, melynek jellegzetes tünetei az egész csontvázrendszert érintik. Ezek a koponya késői csontosodása, apláziás vagy hypoplaziás claviculák és egyéb, komplex fogászati abnormitások. A Williams- Beuren szindrómához hasonlóan a CCD korai felismerésének számos nehézsége van, mert a craniofaciális abnormitások csak felnőttkorban válnak egyértelművé. A páciensnél hypoplasztikus középarc, a mandibula relatív prognathiája, a claviculák hiánya miatt anterior irányban összeérinthető vállakat észleltünk. A vizsgálat perzisztáló tejfogakat, előtörésben visszamaradt számfeletti fogakat valamint részlegesen és szabálytalanul előtörő maradó fogak okozta rendellenes occlusiot mutat. Tipikus fogazati jegyek, a második, maradó moláris előtörése együtt a perzisztáló tejfogakkal és az alsó metszők közötti nagy diasztéma. A klinikánkon kezelt betegnél a szájsebészeti beavatkozás első lépcsőjében a számfeletti fogakat folyamatosan eltávolítottuk a perzisztáló tejfogakkal együtt. Ezt követően került sor az előtörést nem mutató maradó fogak feletti corticalis csont elvékonyítására. Az orthodontiai kezelés részeként a fogívet tágítottuk. Kivehető készülék segítségével tágítottuk a keskeny maxillát és a mandibuláris ívet, és a tervezett Delaire maszkkal a felső állkapocs visszamaradott növekedését kompenzáltuk. Időszakos funkcionális rehabilitációt részleges fogpótlással oldottuk meg. Az állkapcsok teljes kifejlődését követő terápiás célok az implantátumok és hidak alkalmazása. A betegség genetikai vonatkozásai okán a gyerek szüleit is kivizsgáltuk. A betegség genetikai jellege miatt a beteg édesapja is vizsgálatra került, és CCD tüneteit mutatta, ezért ő is komplex fogászati kezelést kapott.

A hivatkozott esetek és a vonatkozó irodalom is alátámasztja a CCD korai diagnózisát és interdiszciplináris kezelésének szükségeségét.

SUMMARY

Williams-Beuren syndrome (WS) is a genetic condition, with an incidence of 1 in 20000-50000 live births, consisting of supravalvular aortic stenosis, characteristic dysmorphic facial features named "elf face" and mental retardation. Early diagnosis of the syndrome is important since many of its features require treatment, and the prognosis can be dramatically improved by early recognition and management. This developmental disorder is well known to be clinically heterogeneous, making it difficult to diagnose it based on the clinical picture. However, genetic testing is expansive and it is not cost effective to screen all patients based on clinical suspicion. Our goal was to develop a novel clinical screening method, which is sensitive, specific, inexpensive and readily available. We performed cephalometric analysis and dental evaluation of 33 genetically proven WS patients, and 100 age matched normal controls. Cephalometric analysis of soft tissues showed in WS patients that with normal SNA, SNB and ANB angles, the lips were in front of the e-line by Ricketts. This finding was present in all WS patients, while in none of the age matched controls. No other differences were found between WS and control patients. This cephalometric finding is specific and sensitive for WS and can be used in the diagnostic procedure of the disease, while none of the conventional dental evaluations are useful.

Clinical diagnosis of Williams syndrome can be a challenge at an early age of the patients if none of the characteristic cardiovascular features, i.e. supravalvular aortic stenosis or pulmonary artery stenosis, are present. Our second aim was to demonstrate the changes of cardiovascular lesions during the postnatal development of Williams patients and to follow all cardiovascular findings beyond the most common ones. The cardiovascular status of 29 patients with Williams syndrome -mean age 12.8 years- were retrospectively recorded in correlation with the patients` age. Cardiovascular diagnoses changed in the majority (72.4 %) of patients. Interestingly, 44.8 % of the patients had periods with no reported cardiovascular disease. Furthermore, 65.5 % of the patients experienced periods when none of the typical cardiovascular lesions, i.e. diffuse or localized supravalvular aortic stenosis and/or pulmonary artery stenosis were detected. Spontaneous regression and progression of both supravalvular aortic stenosis and pulmonary artery stenosis were observed. An unexpectedly high frequency (41%) of mitral valve disorders was found.

Our study showed that temporary absence of and changes in cardiovascular findings are frequent in Williams syndrome. These results could contribute to the refinement of diagnostic

criteria and recommendations for cardiovascular follow-up of patients with Williams syndrome.

Cleidocranial dysplasia another genetic conditions with oral manifestations (CCD) is an uncommon generalized skeletal disorder characterized by delayed ossification of the skull, aplastic or hypoplastic clavicles and serious, complex dental abnormalities. There are many difficulties in the early diagnosis of CCD, as a majority of the craniofacial abnormities becomes obvious only during adolescence. In the present case a hypoplastic midface, a relative prognathia of the mandible and close approximation of the shoulders in the anterior plane were the conspicuous extraoral findings. Prolonged exfoliation of the primary dentition, unerupted supernumerary teeth and the irregularly and partially erupted secondary dentition produced occlusional anomalies. The presence of the second permanent molars together with the primary dentition and wide spacing in the lower incisor area were typical dental signs. Gradual extraction of the supernumerary teeth and overretained primary teeth was the first step of oral surgery. This was followed by a surgical exposure of the unerupted teeth by thinning of the cortical bone. Orthodontic treatment aimed parallel growth of the jaws. Removable appliances were used to expand the narrow maxillary and mandibular arches and a Delaire mask compensated the lack of the sagittal growth of the upper jaw. Temporary functional rehabilitation was solved by partial denture. When the jaws have been fully developed, implant insertions and bridges are the therapeutic measures. Because of the genetic nature of the disease, the patient's parents were also examined. The father also showed features of CCD, and received appropriate treatment, again, in cooperation with other specialities.

The reported cases and the literature data support the importance of the early diagnosis and interdisciplinary treatment of CCD.

I. INTRODUCTION

Williams-Beuren syndrome (WS) is a genetic condition. It is a multisystem developmental disorder, which is predominantly sporadic, although some families have been reported to show autosomal dominant inheritance with varying penetrance (Sadler et al, 1993; Morris et al, 1993; Ounap et al, 1998). The incidence of WS is estimated to be approximately 1 in 20 000 - 50 000 live births (Greenberd, 1990). It was first described by Williams in 1961, consisting of supravalvular aortic stenosis, characteristic dysmorphic facial features named "elf face" (wide mouth with long phyltrum and thick lips) (Fig. 1) and mental retardation (Williams et al, 1961). Other clinical manifestations include joint contractures, transient infantile idiopathic hypercalcemia, growth retardation, visuospatial cognitive deficits, gregarious personality, frequent dental anomalies, and primary or secondary hypertension and cardiovascular disorders. The latter findings are classified as an elastin arteriopathy (Beuren et al, 1962, Onis Vilches et al, 1998, Morris, 1998). The syndrome is caused by a submicroscopic deletion in chromosome 7 implicating the 7q11.23 region (elastin locus) (ELN; 130160) (Ewart et al, 1993; Hockenhull et al, 1999; Mila et al, 1999). A high frequency of unequal chromosomal crossovers is implicated as the underlying mechanism of the deletion responsible for Williams-Beuren syndrome (Urban et al, 1996, Dutly et al, 1996).

Early diagnosis of the syndrome is important since many of its features require treatment, and the prognosis can be dramatically improved by early recognition and appropriate management (Bruno et al 2003). This developmental disorder is well known to be clinically heterogeneous, making it difficult to diagnose it based solely on the clinical picture (Tarjan et al, 2003). However, genetic testing is expansive and it is not cost-effective to screen all patients based on the clinical suspicion since the diagnostic genetic finding is not detectable on routine and relatively inexpensive chromosomal analysis. Moreover, many patients are undiagnosed until a serious complication develops, which might have been preventable by early diagnosis and treatment (Eronen et al, 2002).

In many cases, physical manifestations are subtle and may not be apparent at an early age, making diagnosis difficult in infants and young children who lack classic manifestations such as supravalvular aortic stenosis and hypercalcemia. Clinical suspicion is essential because the diagnostic genetic finding is not detectable on routine chromosomal analysis. Furthermore, early diagnosis allows for earlier detection and treatment of developmental, behavioral, and medical problems.

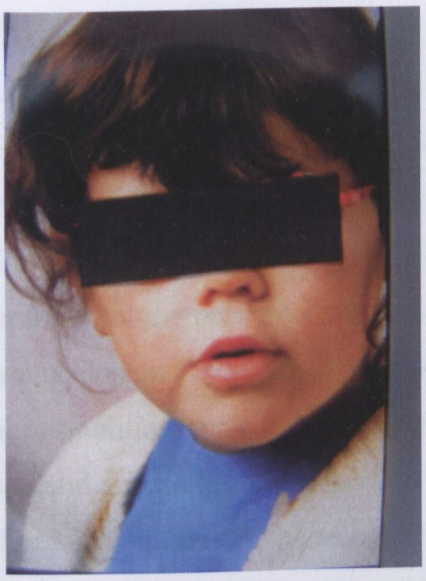
Our first goal was to develop a clinical screening method, which is sensitive, specific, inexpensive, and readily available, and thus, is able to contribute to the identification of patients in whom genetic testing would be cost effective.

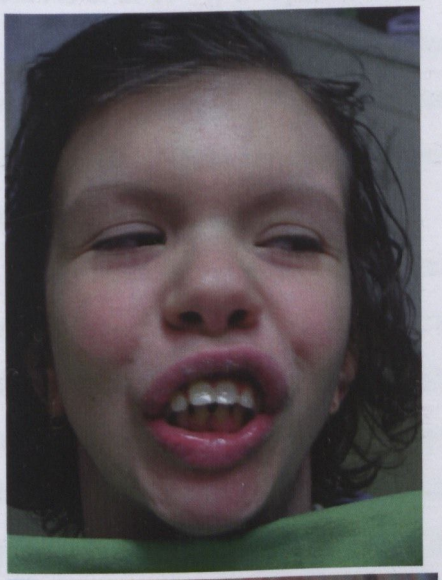
Our first hypothesis was that due to the known dysmorphic facial features and frequent dental anomalies, cephalometric analysis and dental examination can be useful in the early diagnosis of Williams syndrome.

Since dysmorphic signs may be subtle, especially at a young age, and hypercalcaemia may be absent or not recognized (Mass et al 1993, Boraz et al 1991). Therefore, in many cases, the diagnosis of Williams-Beuren syndrome is easily missed if the typical cardiac defects –supravalvular aortic stenosis (SVAS), supravalvular pulmonary stenosis (SVPS) or pulmonary artery stenosis (PAS) - are not present or are not detected. Delayed diagnosis makes individualized early educational intervention and medical management of Williams-Beuren syndrome patients difficult and may create emotional distress in their families as well. The frequency of different types of cardiovascular disorders related to Williams-Beuren syndrome is well known (Lopez-Rangel et al 1992, Wessel et al, 1994) and the natural history of SVAS and PAS in Williams-Beuren syndrome patients has been investigated in several studies (Halladie-Smith et al 1988, Kim et al, 1999). However, no studies are available to date to address developmental changes in the full spectrum of cardiovascular disorders in Williams-Beuren syndrome patients.

Therefore, the second aim of the present study was to provide additional data and to improve the clinical diagnosis of Williams-Beuren syndrome by long-term follow-up of all cardiovascular lesions in Williams-Beuren syndrome patients.

Similarly to Williams-Beuren syndrome, cleidocranial dysplasia (CCD) is an uncommon generalized syndrome with marked oral manifestations. It is a skeletal disorder with pathognomic anomalies of the cranial vault and clavicles (Regezi et al 1995, Golan et al 2003). The anomaly is characterized by delayed ossification of the skull, aplastic or hypoplastic clavicles and serious, complex dental abnormalities (Golan et al 2003, Kanda et al 1995). It occurs with equal frequency among males and females and no racial predilection can be observed (Koch et al 1978, Golan et al 2002). Skull deformity comprises delayed closure of the fontanelles and sutures (Hultkranz 1908). The head is brachycephalic with pronounced





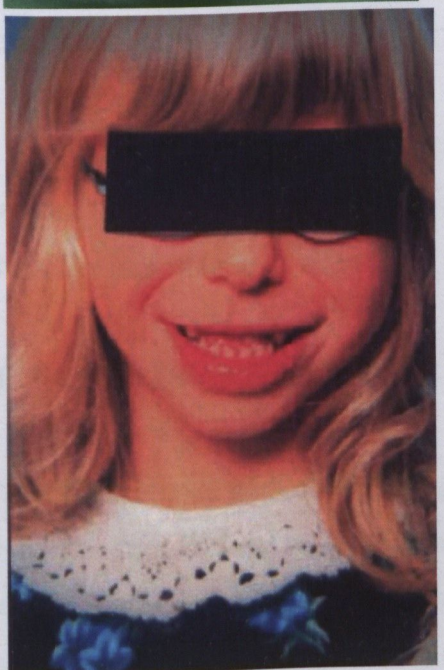


Figure 1. Typical facial appearance of Williams syndrome patients showing wide mouth with long phyltrum and thick lips (published with parent's permission).

frontal, parietal and occipital bossing (Shen et al, 2000). Midface retrusion, broad based nose and ocular hypertelorism are also frequently present (Kanda et al 1995, Kreiborg et al 1999). Complete or partial absence of clavicular ossification and the associated muscle defects will result in a long appearance of the neck and markedly dropped, hypermobile shoulders. Prolonged exfoliation of the primary dentition, unerupted supernumerary teeth and failure of eruption of the permanent teeth together with maxillary hypoplasia, produce severe malocclusion (Jensen et al 1990, Richardson et al 1994). The teeth have inherent abnormalities; such as dilaceration, gemination, enamel and cementum hypoplasia. Other skeletal anomalies have also been associated with these major clinical features. Defects of the thoracic vertebrae, kyphoscoliosis, affected pelvis, long bones and fingers may likewise occur (Jarvis et al 1974, Cooper et al 2001).

CCD is inherited in an autosomal dominant way with complete penetrance and variable expressivity. The condition is caused by mutations in the runt-related transcription factor 2 (RUNX2) gene located on chromosome 6p21 (Golan et al 2002, Mundlos et al 1997, Yoshida et al 2002).

There are many difficulties in the early diagnosis of CCD (Golan et al 2004). About one third of the cases are sporadic and appear to represent new mutations; these patients have unaffected parents (Otto et al 2002). The most striking marker, the extreme shoulder mobility, is not always expressed, and a majority of the craniofacial abnormities becomes obvious only during adolescence. The ideal treatment time is determined by the root development and bone quantity. Early recognition of the disorder is advantageous for successful therapy and rehabilitation.

The aim of this part of the study was to describe the typical signs and symptoms and explore the possibilities for combined surgical, orthodontic and prosthetic treatment. Thus, to show the importance of team-work including the dentist and other medical specialities.

II. PATIENTS AND METHODS

39 patients with clinical suspicion for Williams syndrome were referred to the 2nd Department of Pediatrics of the Semmelweis University in Budapest, Hungary by pediatricians or cardiologists. Mean age of the patients was 13.9 years (6-23 years). Age matched healthy patients served as controls (n = 100). Fluorescent in situ hybridyzation (FISH) was carried out using peripheral lymphocytes as described before (Urban et al 1996).

Based on a Williams-Beuren syndrome population incidence of 1/25 000 (Ewart et al, 1993, Madisen et al, 1987), the expected number of Williams-Beuren syndrome patients in the Hungarian population between 0-24 years is approximately 133. Therefore, the patients participating in this study represented approximately 22 % of the estimated Hungarian Williams-Beuren syndrome population. Dental evaluations were performed at the Pedodontic and Orthodontic Department of the Semmelweis University in Budapest, Hungary. Cephalograms were obtained and cephalometric analysis of the soft tissues was performed on all patients according to standard methods (Walker 1994, Ricketts et al 1976). The reader of the cephalograms (GB) was blinded regarding the results of FISH. Head postures were standardized by using supporting plates. Detailed dental and periodontal examinations were carried out by using sharp explorers and mirrors. CPITN indices were used to establish periodontal condition. The study was approved by the Institutional Review Board (ethic committee). We used the chi-square test to evaluate for statistically significant differences between the two patient groups.

29 patients with Williams-Beuren syndrome were included for detailed cardiac evaluation and cardiology follow up. These patients ranged in age between 2-23 years, with a mean age of 12.8 years. There were 17 (58.6 %) female and 12 (41.4 %) male patients.

Cardiac evaluation

We collected data relating to the cardiovascular status of the patients during their life span, regardless of whether the diagnosis of Williams-Beuren syndrome had already been made or not. Cardiac diagnosis was established based on physical examination, ECG, chest X-ray and echocardiography. The cardiovascular diagnoses were established in different hospitals, but all results were verified at the Semmelweis University, Budapest and the Hungarian Institute of Cardiology using standardized cardiac evaluation criteria. The examination protocol was identical for all patients and visits. The method used for blood pressure measurements were averaging the results of three measurements with a non-invasive method using a sphygmomanometer with the appropriate size cuff. The definition for hypertension was blood pressure values above the 95th percentile for the patients' age. Routine cross sectional echocardiography studies were carried out using Acusion XP 128 and 600 echocardiographs with the latter having adaptive pulse wave Doppler facility. For all

patients at least one echocardiographic follow-up examination was performed. The average number of echocardiographic studies was 7.5 occasions per patient.

SVAS was diagnosed by positive echocardiography results: at least 2 m/s peak flow velocity or 16-mmHg peak instantaneous gradient. Aortic coarctation was detected from suprasternal long-axis view, as a localized narrowing of the thoracic aorta just beyond the origin of the subclavian artery. Associated findings, such as isthmus hypoplasia, poststenotic dilatation, and diminished systolic pulsations in the descending aorta served to confirm the presence of a significant coarctation. The diagnosis of mitral valve prolapse (MVP) was established when more then 2 mm prolapse of the valve was detected from two different planes and/or during the opening of the mitral valve thickening and the typical fibrillation of the valve was detected. Peak instantenous gradient was measured and color Doppler was used for the assessment of mitral valve insufficiency (MVI). PAS was identified by comparing the flow velocities at the pulmonary valve and at the distal right and left pulmonary arteries. If the difference was >1,8 m/s the patient was classified as having PAS. Angiography was performed if indicated by disease severity.

Genetic analysis

Total genomic DNA was isolated from peripheral blood leukocytes of Williams-Beuren syndrome patients, their parents and siblings using a previously published method (Madisen 1987). Genetic analysis of 8 patients: 1124, 1151, 1081, 1093, 1089, 1138, 1420, 1172 from this cohort has previously been published (Urban et al 1996). These and all the additional patients were genotyped for the following 6 deletion specific markers: ELNi1 (Kaplan et al 1995), ELNi18 (Dib et al 1996), LIMK1GT (Kaplan et al 1995), D7S613, D7S489 (Foster et al 1993) and D7S1870 (Gilbert-Dussardier et al 1995). Fluorescently labeled PCR products were analyzed using an ABI Model 310 automated genetic analyzer and results were scored using the Genotyper 2.1 software.

III. RESULTS

Cephalometric analysis and dental evaluation

Williams syndrome was positively identified in 33 of the 39 patients by FISH. This represents 50 % of all known Williams syndrome patients identified to date in Hungary. Dental aplasia was found in 91 % of the WS patients, while in 6 % of the controls ($p < 0.001$).

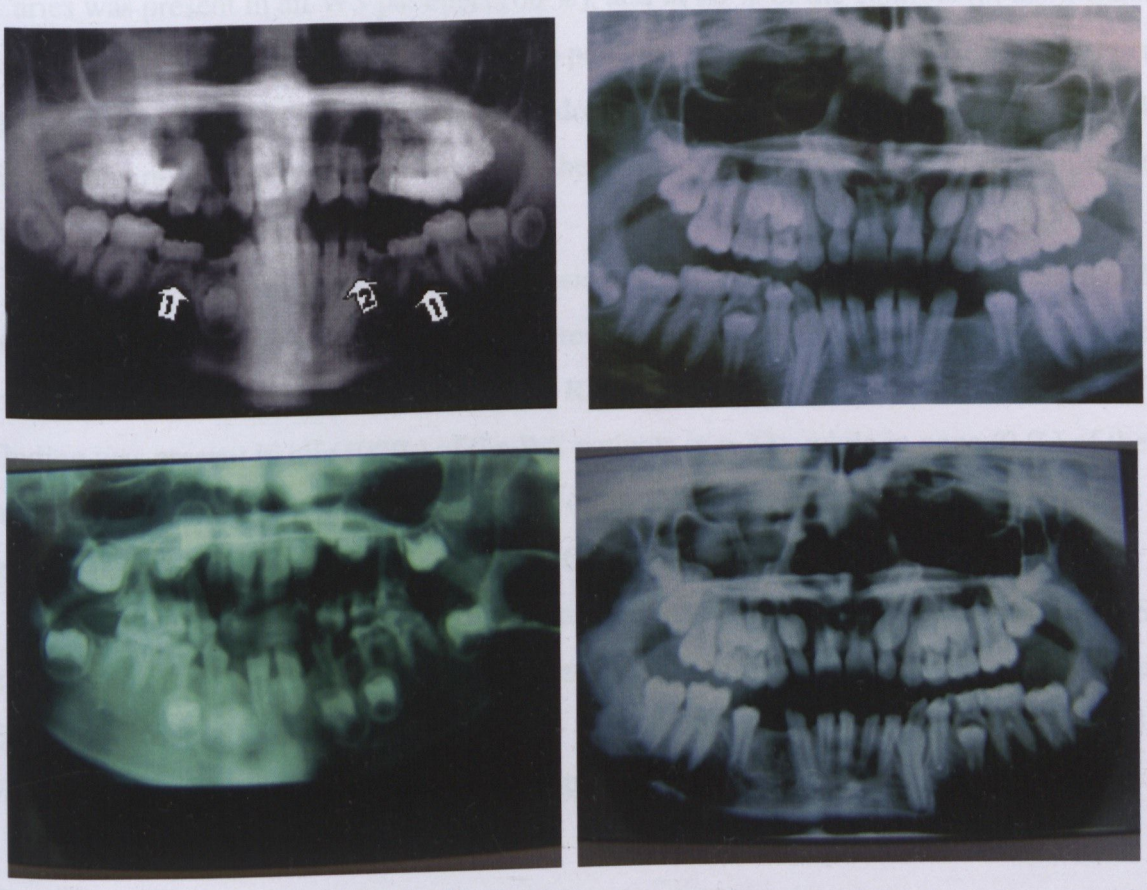


Figure 2. Orthopantomogram tomographic radiography of a typical Williams syndrome patients showing aplasia and tooth resorption anomaly, with fan shaped positioning of the front teeth.

Caries was present in all WS patients (100 %), and in 96 % of the controls (p: n.s.). Calculus was found in 30.3 % of Williams syndrome patients, while 2 % of controls ($p < 0.001$), and gingivitis was seen 93.9 % of Williams syndrome patients vs 26 % of controls ($p < 0.001$). Supranumeral teeth were found in none of the WS patients, while in 1 % of the controls (p: n.s.).

In WS patients, cephalometric analysis of soft tissues showed that SNA, SNB, ANB angles were normal (82, 80, and 2 degrees, respectively), and the lips were in front of the line of harmony (esthetic line or E - line) by the Ricketts analysis (fig 3-4) (Ricketts 1976). This finding was present in all (100%) of the WS patients ($n = 33$), while in none (0 %) of the age matched controls ($n = 100$). The frequency of the findings was statistically significantly greater in WS patients (Chi-square test, $p < 0.001$).

Cephalometric analysis of skeletal components was not different between the WS and control groups. SNA, SNB, ANB angels were not different between the two groups (mean ± SD: 85.5 ± 4.96, 81.9 ± 4.47, and 3.7 ± 2.34 for Williams syndrome patients, vs 82.7 ± 3.14, 79.8 ± 5.81 and 3.2 ± 4.87 degrees for controls, respectively, p: n.s. for all).

Cardiac evaluation

The average age of the patients included for cardiac workup at the clinical diagnosis of Williams-Beuren syndrome was 5.6 years. The earliest age of diagnosis was one year and the latest was 15 years. Among the patients with mild or no significant cardiac findings, the mean age at the diagnosis was 7.1 years of age. On the other hand, among patients with SVAS or severe cardiac symptoms, the mean age of diagnosis was at 4.5 years of age, which is later than expected. However the T-test did not show a significant difference between the ages of the diagnoses.

All Williams-Beuren syndrome patients but one demonstrated some signs of heart disease. In the majority (72.4 % of patients) the cardiovascular findings changed over time. Ten patients had only one sort of cardiovascular disorder; while 19 patients had multiple defects (fig 5.). One child had only a heart murmur without any signs of organic heart disorders, confirmed by echocardiography.

There were 11 (37.9 %) patients without any signs of aortic narrowing. Eighteen patients (62.1 %) had localized or diffuse narrowing on the aorta, among which SVAS was found in 16 patients (55.1 %). This is somewhat lower than the findings of SVAS by Wessel et al in Williams-Beuren syndrome patients (76,2%) (Wessel et al 1994). Aortic coarctation

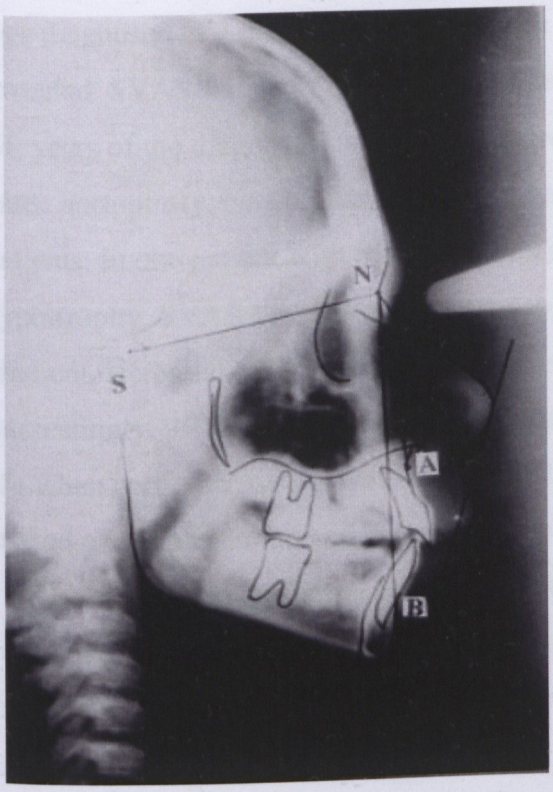


Fig. 3. Cephalogram of a Williams syndrome patient. With normal SNA and SNB angles, the lips are in front of the line of Harmony

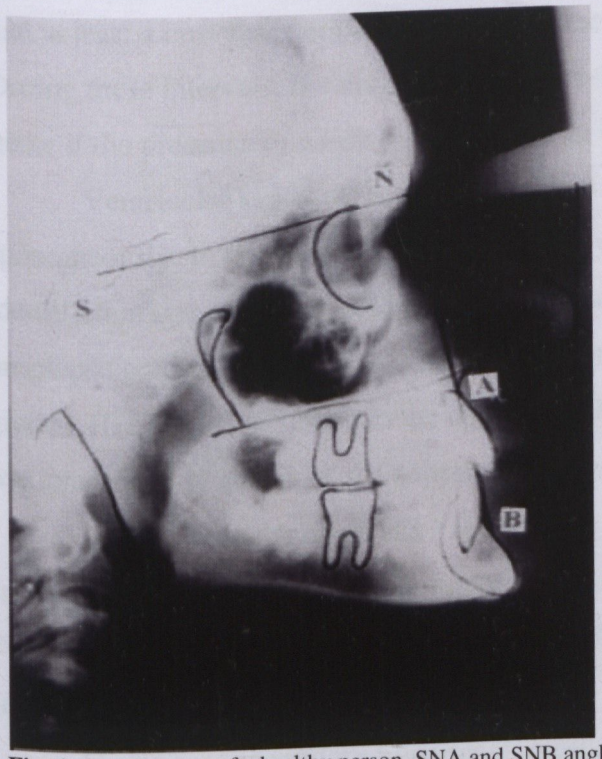


Fig. 4. Cephalogram of a healthy person. SNA and SNB angles are normal, lips are behind the esthetic line (the line connecting the pogonion and the tip of the nose). *S* midpoint of the sella turcica; *N* most anterior point on the frontonasal suture; *A* position of the deepest concavity on the anterior profile of the maxilla; *B* position of the deepest concavity on the anterior profile of the mandibular symphysis

was diagnosed in 2 patients (6.89 %) and in one patient aortic isthmus hypoplasia was revealed. SVAS showed progression in 4 patients (25.0 % of SVAS patients). After 3, 4, and 14, years of the diagnosis successful treatment of severe SVAS in 3 patients was achieved by patch aortoplasty. No surgical complications or residual stenoses were observed in these patients. In one patient with SVAS, the last echocardiography revealed marked left ventricular hypertrophy. SVAS showed spontaneous regression in one patient. In this case the pressure gradient decreased from 44 mmHg to 17 mmHg from his infancy until his 19 years of age. Interestingly, 9/18 (50 %) patients with localized or diffuse aortic narrowing had a period in life when aortic narrowing was not detected; the location of this narrowing that was either missed or not present on serial scans. One patient had a bicuspid aortic valve.

PAS was identified in 5 (17.2 %) patients and in 4 patients the diagnosis of valvular pulmonary stenosis was established. Some type of pulmonary stenosis was established in a total of 8 (27.5 %) patients. PAS detected in early infancy showed regression in all cases.

Either of the two main cardiac signs of Williams-Beuren syndrome, i.e. aortic narrowing or pulmonary stenosis, were detected in 20 (68.9%) patients. At the same time 9 (31.1 %) patients did not demonstrate these cardinal findings. Altogether 19 (65.5 %) patients had at least a one-year period in life when none of these typical symptoms were detected. During these intervals, the diagnosis Williams-Beuren syndrome would have been difficult to make if the presence of cardiac disease was an essential diagnostic criterion.

Ventricular septal defect was noted in 4 patients and in all but one it closed spontaneously. In one case surgical correction was necessary. Atrial septal defect was identified in one child only and it closed spontaneously. In 9 (31.8 %) patients, mitral valve proplapse grade I-II. was found and in 8 patients mitral valve proplapse associated with MVI grade I-II. In 3 patients MVI in the absence of MVP occurred. A disorder of the mitral valve was present in 12 (41 % of the patients). The average age of the detection was 9.7 years.

Diffuse vascular disorders - renal artery stenosis, hypoplasia of the left pulmonary artery, and hypoplasia of the abdominal aorta - were identified in 4 (13.7 %) patients. Naturally, these problems were only revealed if the clinical condition of the patient justified angiography.

In one case secondary hypertension caused by renal artery stenosis was revealed. Bilateral bypass surgery was performed and therapy was supplemented with an alpha adrenergic-receptor antagonist (clonidine), angiotensin-converting enzyme-inhibitor (enalapril), beta-blocker (metoprolol) and antithrombotic (acetylsalicylic-acid) treatment. This agrees with the findings of Rose et al, who suggested that generalized arteriopathy is a more

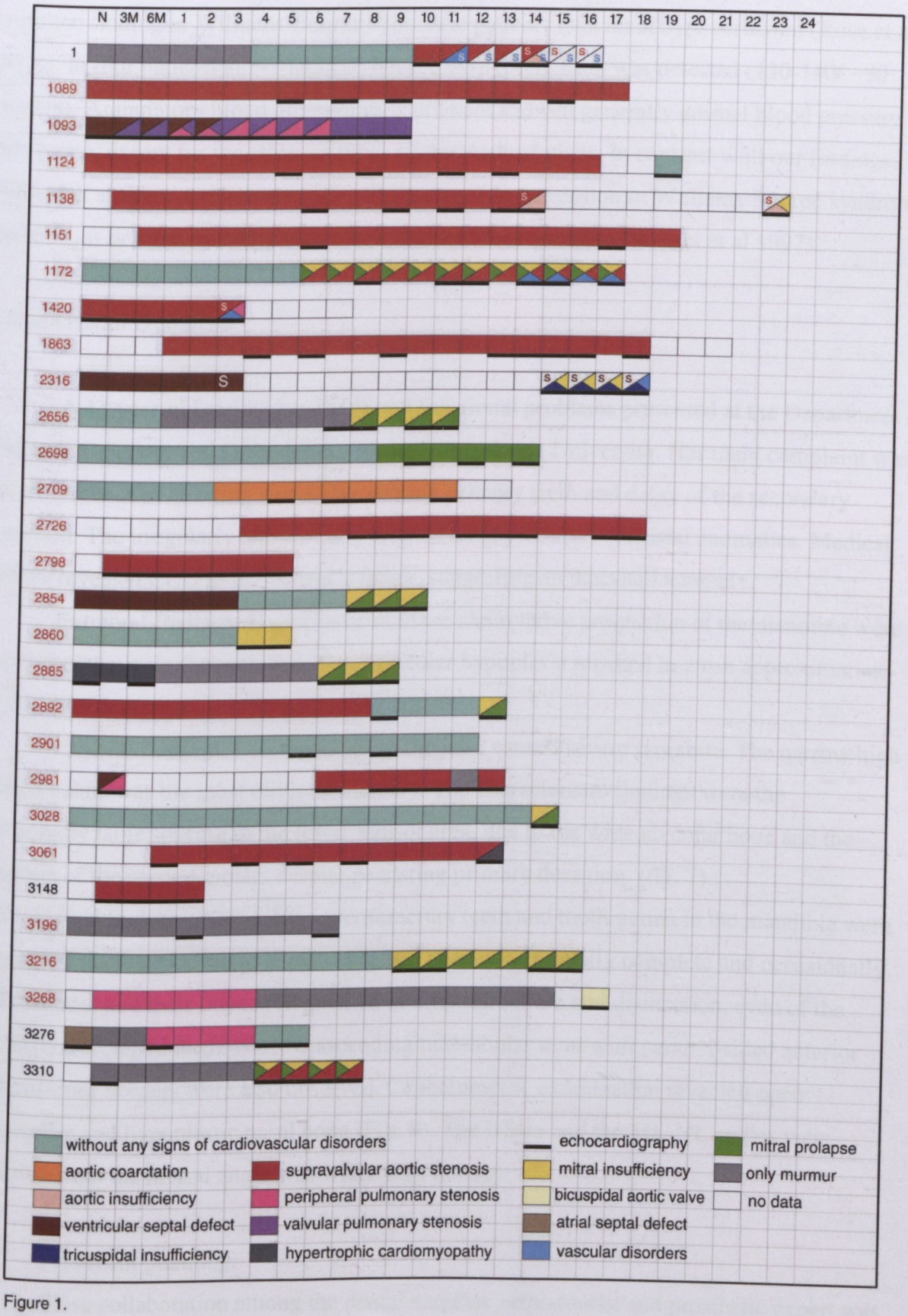


Figure 1.

common finding in Williams-Beuren syndrome patients than renal hypoperfusion (Rose et al 2001). In four patients stress-induced borderline hypertension was detected (130-140/ ~90 mmHg). Ambulatory blood pressure measurement showed generally normal blood pressure in this group, except for the stressful times of the medical visits. In contrast with our findings, Wessel et al found a relatively high (40 %) rate of hypertension in Williams-Beuren syndrome patients, as defined by >95 percentile of normal blood pressure (Wessel et al 1997).

Cleidocranial Dysplasia

A 13 year-old girl with esthetic and functional problems presented at the Department of Pediatric Dentistry and Orthodontics of the Semmelweis University. Her main complaint was the disturbance of chewing caused by missing primary teeth and delay of the secondary dentition. The irregularly and partially erupted teeth produced occlusial anomalies. Medical history revealed CCD in the patient's father, suggesting an inherited anomaly.

Extraoral findings. Hypoplastic midface and relative prognathia of the mandible were the conspicuous skull anomalies. The clavicular hypoplasia resulted in close approximation of the shoulders in an anterior plane (Fig. 6).

Intraoral findings. Discrepancies of the jaws caused severe crossbite. The narrow high arched palate was the most obvious anomaly. The characteristic findings were the abnormally large spacing in the lower incisor area, due to the wide alveolar bone and the eruption of the second molars despite persisting primary dentition (fig. 7).
Radiological findings. Numerous supernumerary teeth and tooth germs in the mandible were diagnosed via the panoramic X-rays (Fig. 8). They were partially complete and occasionally rudimentary, and their impaction resulted in eruption failure and dislocation, even of the normally developed teeth. Narrow ascending mandibular rami with parallel-sided anterior and posterior borders were also observed. Cephalometric examination revealed open fontanelles and hypoplastic nasal bone (Fig. 9). The NSBa and the ML-NL angles were narrower, and the incisal angle was wider than normal.

Treatment planning.

Close collaboration among the dental surgeon, orthodontist and prosthetic expert was necessary. The aim was an adequate esthetic and functional reconstruction.

Proband

Fig. 6. Hypermobile shoulders, aplastic clavicule.

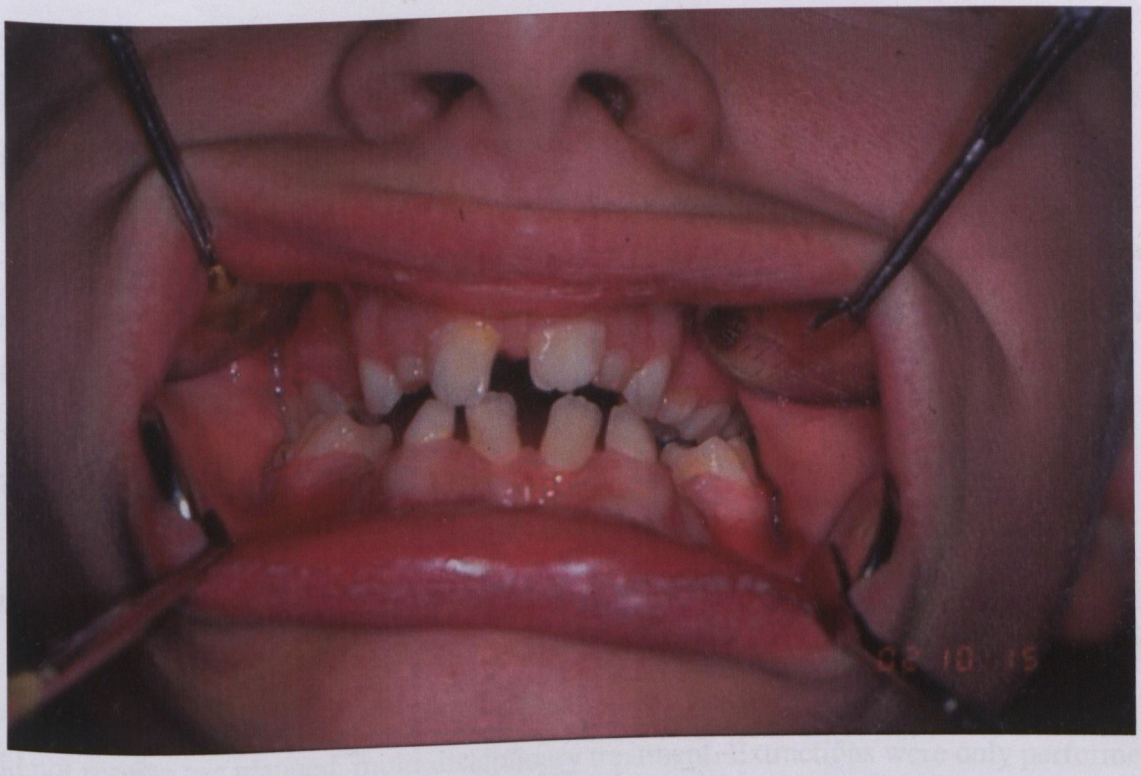


Fig. 7. Large spacing in the lower incisor area.

Fig. 6. Hypermobile shoulders, aplastic clavicule.

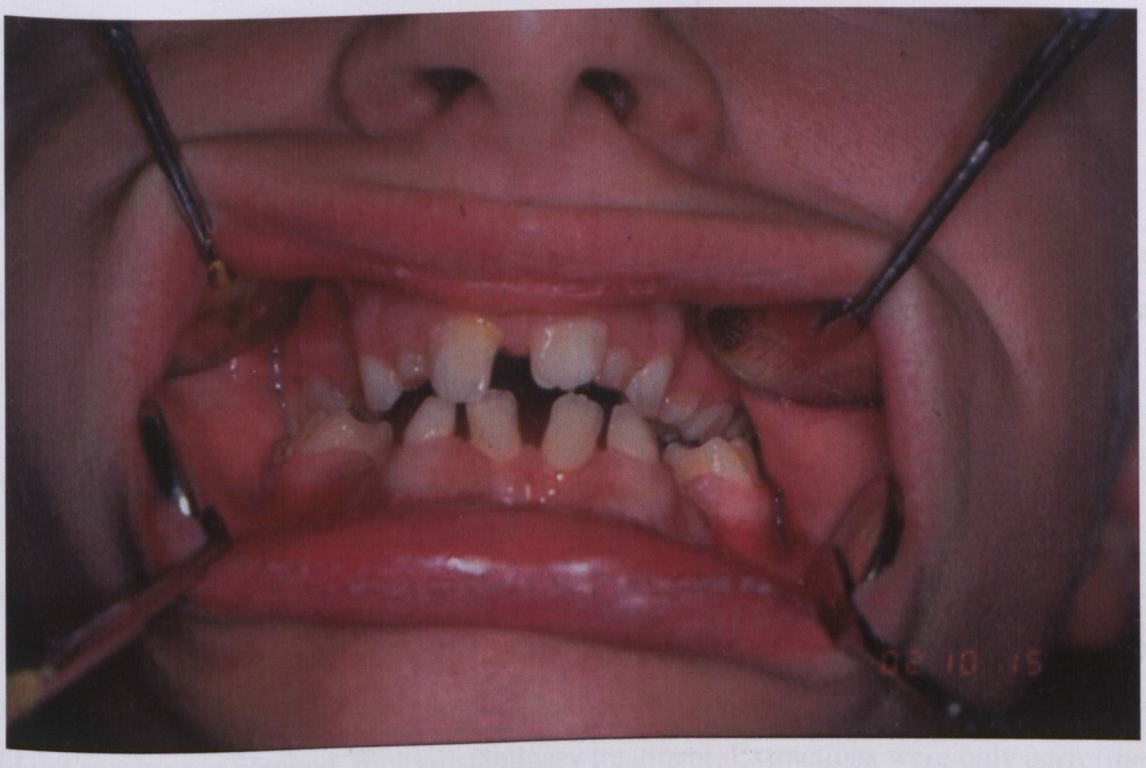


Fig. 7. Large spacing in the lower incisor area.

Oral surgery. The first step was a gradual extraction of the supernumerary teeth, and over-retained primary teeth, when the root formation of the succedaneous teeth was appropriate. A majority of the tooth germs were deformed and rudimentary. Microdontia, twinning, dilacerations, hypoplastic enamel and cement were the most frequent findings. The next step was surgical exposure of the unerupted, well-developed teeth, by thinning of the cortical bone. The supernumerary mandibular canines were not removed because of the close proximity of the inferior alveolar and mental nerves.

Orthodontic treatment. The aim was to achieve parallel growth of the jaws and preparation of the remaining permanent teeth for prosthetic treatment. The planned fixed bridges required sufficient pillar teeth and correction of their axes. The first stage of the orthodontic treatment was a transversal expansion of the narrow mandibular arch by a Y-shaped screwed appliance to make place for the eruption of the secondary teeth. This mandibular anomaly resulted from the earlier, inadequately timed extractions of the primary teeth. At the same time another removable appliance was used to expand the maxilla by opening the midline sutura. The next phase was a multiband treatment of the maxillary dental arch and application of a Delaire mask to compensate for the lack of the sagittal growth of the upper jaw, so as to avoid the mandibular prognathia.

Prosthetic treatment. Temporary functional rehabilitation was solved with a partial denture. When the jaws are fully developed implant insertion and bridges are the final steps of the therapy.

Father

Oral surgery: extraction of the decayed roots and supranumerary teeth were performed to prepare the patient for prosthetic treatment.

Prosthetic treatment: fixed and partially removable dentures were prepared to restore functionality, since the patiients' supranumerary teeth were not extracted at younger age. He did not receive pre planned, multi disciplinary treatment. Extractions were only performed "as needed".

Orthodontic treatment was not considered because of the patient's age (50 years).

IV. DISCUSSION

Because of its highly varying phenotype, it can be problematic to recognize Williams syndrome. In many cases, physical findings are subtle and may not be apparent at an early

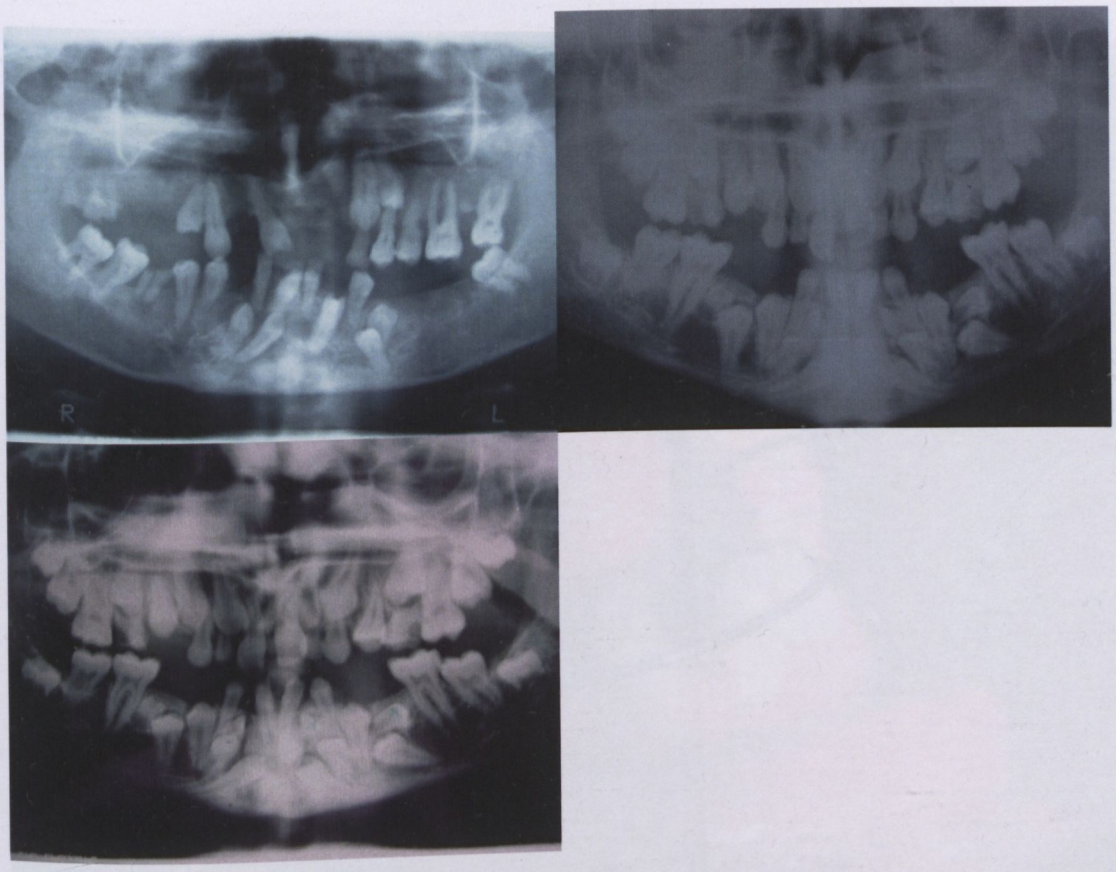
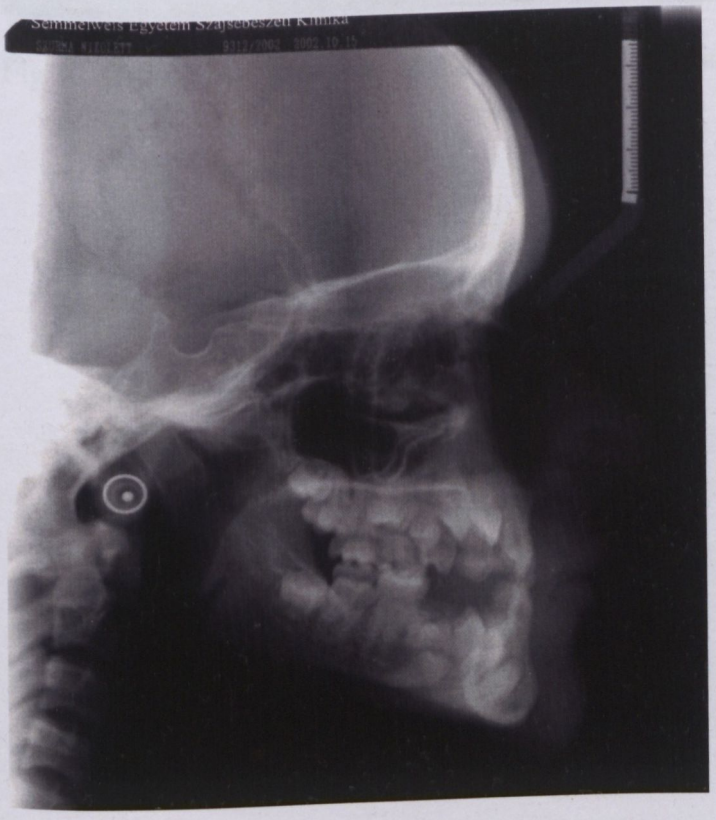


Fig. 8. Supernumerary teeth and tooth germs in the mandible of the proband and her father.



Kefalometria		A
Mérések	Ortognát arc, normál értékei	Dátum
SNA	82	91,2
SNB	80	88,6
ANB	2	2,6
SNPq	81	89,3
NSBa	130	113,3
Gn-tgo-Ar	126	122,3
N szög	58	60,5
H szög	8	10,5
ML-NSL	32	23
NL-NSL	8,5	8,3
ML-NL	23,5	14,6
N-Sp' (mm)		72,6
Sp'-Gn (mm)		90
N-Sp' / Sp'-Gn	100 % 79	79
T-⊥ (szög)	131	171
⊥-NA (szög)	22	3,1
T-NB (szög)	25	-5
⊥-NA (mm)	4	-1,7
T-NB (mm)	4	-1,7
Pg-NB (mm)		1,8
T-NPg (mm)		-3

Fig. 9. Open sutures and hypoplastic nasal bone.

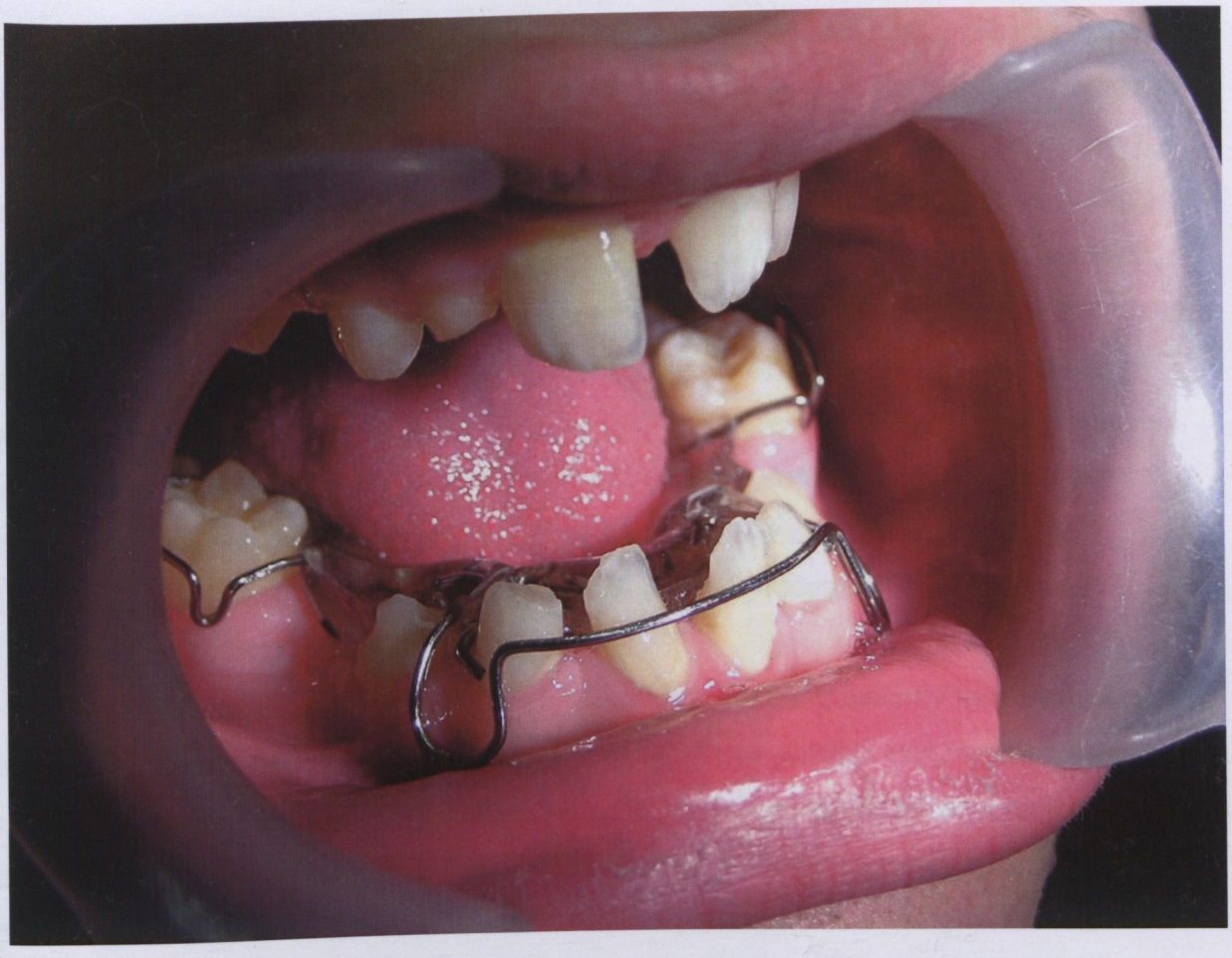


Fig 10. Orthodontic treatment of the proband with removable device, y shaped plate.

age, making diagnosis difficult in children who lack classic manifestations (Huang et al 2002). Clinical suspicion is essential because the diagnostic genetic finding is not detectable on routine chromosomal analysis. Furthermore, early diagnosis is important as it allows for earlier detection and treatment of developmental, behavioral, and medical problems. Despite the fact that the characteristic facial structures in Williams syndrome have been described, and facial dysmorphology is considered to be a major diagnostic feature in WS, suitable and completely reliable diagnostic procedures in WS have not been reported. It has been attempted before, to use cephalometric analysis in the diagnosis of WS, but both prognathia and retrognathia were seen in WS patients, and common skeletal components were not dominant enough to characterize the facial dysmormphology in Williams syndrome (Hertzberg et al 1994). Therefore, it was concluded that cephalometry is of little use (Hertzberg et al 1994, Mass et al, 1993).

We found dental aplasia in our WS patients much more frequently than Hertzberg et al in a previous study (Hertzberg et al 1994). We feel that one possible explanation for that could be that unlike us, Hertzberg did not perform genetic testing. Because of the complex nature of the syndrome and its diagnostic difficulties, it is therefore possible that some of their patients did not have WS. Caries was more frequently present in our WS patients than in those of Hertzberg et al, but of note is that caries was also present in 96% of our control population. It is well known that caries is a more frequent problem in the pediatric population of Hungary than in the United States (Hertzberg et al 1994, Boraz et al 1991).

Our most important finding was that cephalometric analysis of soft tissues showed that with normal SNA, SNB and ANB angles, the lips were in front of the line of harmony (fig 3-4). This finding was present in all WS patients (n = 33), while in none of the age matched controls (n = 100). Consequently, this finding was specific and sensitive for WS. We feel that this finding, especially when dental aplasia is present, can be used to identify patients in whom genetic testing for WS would be cost effective. Cephalometric analysis of soft tissues can be used after 3-5 years of age, after facial soft tissue structures are developed and stable. Early diagnosis is a key component in the successful management of Williams syndrome patients since some of the conditions, associated with WS such as aortic stenosis, require early treatment (Onis Vilches 1998, Bruno et al 2003). Also, infant dental care, nutrition counseling, and restorative care are extremely important for maximizing the quality of life for patients with Williams syndrome (Boraz et al 1991). We suggest that the results apply only to probands from Hungary, and should not be generalized to races other than European (white).

Cardiovascular disease is an important cause of morbidity and even mortality in Williams-Beuren syndrome (Wessel et al 2004). It is known that cardiovascular disease in Williams-Beuren syndrome is not stable throughout postnatal development. Several studies have focused on the main vascular components of Williams-Beuren syndrome, SVAS and PAS (Wessel et al 1994, Halladie-Smith KA 1988, Kim et al 1999). All these studies showed that PAS tends to improve spontaneously, while SVAS was generally found to be progressive. Progression of SVAS was found to be significant in patients with high initial pressure gradients but not in patients with mild pressure gradients (Wessel et al 1994). We earlier showed that the severity of supravalvular aortic stenosis is significantly greater in male than in female patients (Sadler et al 2001). This difference was not accounted for by differences in height, weight, body mass index, or head circumference. The clinical diagnosis of Williams-Beuren syndrome was made at a significantly younger age in male patients. Earlier diagnosis was made partly because of increased incidence and severity of cardiovascular disease (Sadler et al 2001).

Our study expands these initial findings in several respects. First, we have followed the whole spectrum of cardiovascular anomalies in Williams-Beuren syndrome rather than focusing only on SVAS and PAS. Cardiovascular findings changed during postnatal development in 72.4% of our patients. The study shoWilliams-Beuren syndrome that in addition to the major cardiac features of Williams-Beuren syndrome, the severity of other cardiac anomalies can also change over time. As regression and progression were both frequent observations, these results emphasize the importance of regular cardiac follow-up regardless of the presence or absence of cardiovascular findings. Our work confirms earlier findings suggesting that occasional spontaneous improvement of SVAS exists (Wessel et al 1994, Halladie-Smith et al 1988, Kim et al 1999). Our results furthermore demonstrate that a large proportion of Williams-Beuren syndrome patients (75.8%) have periods in life with no detectable heart disease. This finding is unlikely to be due to the study design, since all results were verified at the Semmelweis Medical School and the National Institute of Cardiology using standardized cardiac evaluation criteria and the examination protocol was identical for all patients and visits. In addition, we conclude that the mild cardiac disorders, like the often-detected MVP are diagnosed later than SVAS and septal defects. In our study the diagnosis of Williams-Beuren syndrome was often delayed, if the recognition of cardiac disease was delayed.

Although a relatively small sample size and the retrospective character of the investigation are clearly limitations of our study, our results do indicate developmental

changes in the entire spectrum of cardiovascular lesions in Williams-Beuren syndrome patients. Prospective studies using larger patient populations will be necessary to confirm and investigate these findings further.

The prevalence rate of the CCD is 1/1000000, however, many cases are misdiagnosed because of the extreme variability of the skeletal and extraosseal symptoms. As various indicators of CCD are age related, their expression should be taken into account in early childhood. Some apparent signs of the anomaly become evident only during the pubertal growth spurt, and they are often overlooked at the first inspection of the patient (Golan et al 2004).

Golan et al. described the initial craniofacial findings in CCD patients between the ages of 6 and 11 years in order to categorize their reliability for early detection. Some signs could be found in all patients; others were variably expressed (Golan et al 2004).

The typical extraoral symptoms of CCD are rarely manifested in early childhood (Golan et al 2004). The present case was an apparently inherited CCD as her father was also affected. The extreme shoulder mobility caused by the underdeveloped clavicles was a further diagnostic aid. The patient was examined clinically and radiologically and her dental status was evaluated. The frequently reported craniofacial alterations; frontal bossing and quartermoon physiognomy (Hultkranz 1904), were not marked as the patient was at the beginning of puberty; however, a relatively prognathic mandible could be observed.

Dentition anomalies occur in 93.5% of the CCD cases (McNamara et al 1999). Formation, maturation and eruption of the deciduous teeth are usually normal (Regezi et al 1995). Later, the extreme delay of the physiologic root resorption results in prolonged exfoliation of the primary teeth. The permanent dentition is severely delayed and many teeth fail to erupt (Shaikh et al 1998). In this phase, unjustified removal of the deciduous teeth results in a long-lasting edentulousness and the jaw development remains backward. In the present case, the previous therapeutic measures (the early, inadequate removal of the primary teeth) hampered the transversal development of the mandible and caused additional occlusion problems. This underlines the importance of the early diagnosis.

Presence of the second permanent molars together with a primary dentition and wide spacing in the lower incisor area was found as typical dental signs in all cases in a comprehensive CCD study (Golan et al 2004). These pathognomic findings could also be observed in the present case.

Occurrence of supernumerary germs and teeth is not a pathognomic sign of this anomaly. CCD can also affect patients with no supernumerary teeth, or even with missing teeth (Richardson et al 1994). On the other hand, over 20 syndromes and developmental anomalies have been found to be associated with supernumerary teeth, causing greater confusion (Moore et al 2002). In the present case, the jaws were crowded by many supernumerary teeth, which led to severe eruption anomalies.

In CCD, an interdisciplinary treatment approach involving orthodontics, maxillofacial surgery and prosthodontics is obligatory (Becker et al 1997). In the present case, good collaboration between the specialists and the patient provided a promising result.

The reported cases and the literature data support the importance of the early diagnosis of CCD. Manifestation of the apparent signs during the growth spurt of puberty means a missed opportunity for the correct rehabilitation of the patient.

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