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Follow-up of Children with Williams-Beuren Syndrome in Bulgaria

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Abstract

The Williams-Beurens microdeletion syndrome is a distinctive genetic congenital complex of symptoms, affecting the physical, motor and speech development, as well as most of the organs of the body. Sometimes difficult to be differentiated from other rare genetic disorders in early childhood, it can remain unrecognized for many years. Ultimately, an experienced pediatrician can recognize the characteristic symptoms and suspect the condition or can just suspect a rare disorder and refer the patient to a broader genetic screening. After molecular genetic test for confirmation of the disease, the most optimal form of surveillance should be determined. This includes a coordinated multidisciplinary approach in a specialized center and in accordance with the current professional guidelines and recommendations for children with WBS. Early intervention strategies for supporting motor and speech development, as well as training for daily routines maintaining and integration are very beneficial for the patients. Regrettably, there are no such specialized pediatric centers for any patients with complex genetic disorders and intellectual disability in Bulgaria. Guidelines, recommendations and standards for surveillance and management of patients with rare diseases have scarcely been issued and professional information in Bulgarian language is barely accessible. As a result, even if parents of the affected children are aware of the condition and the best healthcare strategies for their child, enormous personal efforts are needed for planning each medical examination, finding each pediatric specialist, and cover all expenses for specific intervention.

Keywords and Phrases: Williams-Beuren Syndrome; Medical Genetic Counselling; Rare Genetic Disorders; Children's Healthcare in Bulgaria

Introduction

The Williams-Beuren syndrome (ICD-10: Q93.82 Williams Syndrome) is a relatively rare congenital disorder, caused by a microdeletion of the 7q11.23 locus in chromosome 7. The size of the deletion may vary, encompassing between 26 and 28 genes, one of which is always the *ELN* gene. The gene encodes the protein *elastin*, which is an essential component of the elastic fibers of the wall of many internal organs and large blood vessels. The Williams-Beuren syndrome (WBS) is a multiorgan, multisystemic disorder, characterized by various symptoms, mild-to-moderate intellectual disability, growth, motor and speech delay, and characteristic cognitive profile. Adapted growth-charts for WBS children and comprehensive recommendations for surveillance of WBS-patients have been issued; a coordinated work-up by a multidisciplinary team in a single specialized healthcare center has proved to be the most beneficial approach for ambulatory follow-up of WBS patients [1-8].

The prevalence of WBS is similar in populations with diverse descent and is approximately 1 in 7 500 births. There is no specific population data for Bulgaria, however, similar numbers must be expected. Despite the similar health problems of WBS patients worldwide, WBS patients as well as other patients with rare genetic diseases in our country, are facing challenges, such as lack of specialized diagnostic, of multidisciplinary teams, of national standards and guidelines for follow-up of patients with special needs. Thus, patients and their families must search for a "small-scale solution" for each specific medical problem from different healthcare providers and professionals, each being focused on a limited number of symptoms but not on the patients as a whole. Most diagnostics, surveillance and intervention expenses must be covered by patients and their families. Furthermore, the healthcare system is completely unprepared for the entering adulthood WBS-patients.

Generally, WBS is clinically recognized during childhood by neonatologists or pediatricians. The most common suggestive findings are heart murmur, supravalvular aortic stenosis, delayed motor and speech development and/or the specific facial phenotype, historically known as the *"Elfin facies"*. Confirmation of the suspected clinical diagnosis is made by either targeted molecular genetic testing, or by common microdeletion syndrome genetic screening. Unfortunately, in Bulgaria most of the patients have barely any counselling afterwards, regarding the nature of the condition or the recommended follow-up procedures. None of the families that sought genetic counselling in our practice was referred to genetic counsellor; they all made an appointment after their own research in the Internet. This manuscript addresses the challenges that five Bulgarian families with a WBS-affected child had to face in order to understand the condition and summarizes the current recommendations for surveillance and management of WBS children that the families received from the genetic counselor.

Clinical Cases

Personal History

Within one-and-a-half calendar years 5 families with a WBS-affected child appointed genetic counselling in our practice, without being referred to it by any healthcare professional. Among the five children, aged from 7 months to 5 years-and-7-months, two are girls and three are boys.

No pathological findings were found during three of five pregnancies. A placental detachment at fifth lunar month (l. m.) was followed-up in one pregnancy. Intrauterine fetal growth retardation was observed during one pregnancy (s. table 1). Childbirth occurred between 35th and 41st gestational week (g. w.) via vaginal delivery in one case; via planned cesarean section due to maternal indications in one case; via emergency cesarean section due to deterioration of cardiac function in the rest three of the cases.

Growth indicators at birth were at the lower half of the nomogram plots: the weight-to-age ratio was between the 1st percentile[1] (-2.95 z-score[2]) and the 15th percentile (-1.04 z-score); the length-to-age ratio was between the 1st (-2.30 z-score) and the 45th percentile (-0.12 z-score); the head circumference-to-age ratio - between the 16th (-0.98 z-score) and the 37th percentile (-0.32 z-score) (according to the standard nomograms of CDC 2000 and/or WHO [9]) (table 1).

One family was referred to genetic testing for WBS after the pediatric cardiologist suggested the diagnosis based on the facial phenotype and supravalvular aortal stenosis, identified shortly after birth. The first clinical presentation of the syndrome in two children was pulmonary stenosis with "congenital heart murmur"; however, at this point WBS was not suspected. These two children, as well as two others, showed signs of motor and/or speech development delay, first noticed by their parents. All parents instinctively assigned their children to early intervention programs with physiotherapist, speech therapists and/or pediatric neurologist/psychiatrists, without knowing the cause of the delay. In three of these cases the healthcare providers recommended genetic testing for clarifying suspected general genetic disorder. One family was referred to genetic testing by a pediatric gastroenterologist, who examined the child regarding feeding problems.

Molecular genetic testing expenses were covered by private funding in four of all five families; the analyses for one child were met by the hospital, to which the family was referred to for diagnostics. Upon receiving test results, none of the families was referred to genetic counselor and none of them received any professional information or recommendations, concerning the WBS. All parents continued their intervention programs on own expenses: five families worked with physiotherapist; two families worked also with speech therapists and three families - with pediatric psychologist or psychiatrist. One family found information on the Internet about our genetic consultation and made an appointment. The rest of the families followed, after being informed from the first family.

Further Clinical Findings

Mild supravalvular aortic stenosis (SVAS) with a peak gradient of 25 mm was identified in one child within the first days after birth. Two children were found to have mild pulmonary stenosis shortly after their delivery. A hemodynamically insignificant foramen ovale was described in one child. Before genetic counselling only one child was regularly followed-up by a cardiologist regarding the SVAS. None of them has ever had blood pressure measurement (table 1).

Before genetic counselling only one child has had regular serum calcium level monitoring. Following genetic counselling, after calcium level testing was recommended, one child was found to have hypercalcemia, as total calcium was found to be 2.72 mmol/L (reference values 2.19-2.51) and ionized calcium (Ca^{2+}) in serum was 1.42 mmol/L (ref. values 1.16-1.32). Normocalcemia was acquired by dietary correction. Three of five children were found to have hypovitaminosis D (Table 1), in contrast with the prevailing scientific data association of WBS with elevated vitamin D levels.

None of the five children had thyroid gland function monitoring prior genetic counseling. Referred to clinical laboratory from our geneticist, one of five children was found to have hypothyroidism, with TSH levels of 9.23 mlU/L (ref. values 0.67-4.16) and fT4 levels of 10.24 pmol/L (ref. values 11.5-22.7) and required hormone replacement therapy. One child showed subclinical hypothyroidism with slightly elevated TSH level, but fT3/ fT4 within normal range and is under regular observation by endocrinologist.

Common finding in our patients were various herniations that required surgical intervention. One child had left inguinal, right inguinal and umbilical hernia; one child had inguinal and umbilical hernia; one child had inguinal hernia only.

No hearing impairment was identified in any of the five children; however, no targeted evaluation besides the neonatal screening was ever done. Two families reported problems with excessive cerumen in their children.

No visual impairment or any other ophthalmological problems were known in any of the children. All of them have visible medial epicanthi. Two children have light-colored irides, which enables observation of the characteristic WBS stellate pattern.

All children demonstrate joint hypermobility, but none of them has spinal or other skeletal deformities and pathological contractures. All children have very elastic skin.

Breastfeeding/feeding difficulties in infancy and early childhood are reported in all families. Two of five children found transition to solid foods a real challenge.

Falling asleep and sleep duration problems are reported in three of the children. These problems were resolved by regular bedtime routines introduced by parents after recommendations by psychiatrists.

Table 1: Summarized phenotypes and clinical data for the five probands with genetically confirmed Williams syndrome. Abbreviations: yrs. - years; mos - months; g.w. - gestational week; CS - Cesarean section; l.m. - lunar month; PVN - per vias naturalis (natural birth mechanism); IUGR - intrauterine growth retardation; WHO - world health organization; BMI - body mass index; HC - head circumference; CVS - cardio--vascular system; BP - blood pressure; SVAS - supravalvular aortic stenosis; TSH - thyroid stimulating hormone.

Patient		**I**	**II**	**III**	**IV**	**V**
Gender and age		Female, 2 yrs. 2 mos.	Male, 5 yrs. 7 mos.	Male, 7 mos.	Female, 5 yrs.	Male, 3 yrs. 3 mos.
Pregnancy, term and mechanism of birth		1st pregnancy; detached placenta V l.m. 39 g.w. Emergency CS	3rd pregnancy; no abnormalities 39+6 g.w. PVN	1st pregnancy; 41 g.w. Emergency CS (heart rate decelerations)	2nd pregnancy; 38 g.w., planned CS (maternal indications)	2nd pregnancy; IUGR; 35 g.w., Emergency CS (heart deceleration)
Neonatal period		No pathological findings	No pathological findings	Neonatal depression, muscular hypotonia, heart murmur with left-to- right shunt and pulmonary stenosis	Neonatal depression; muscle hypotonia; atypical, mild pulmonary stenosis, systolic murmur, persistent foramen ovale	Hemodynamically insignificant *foramen ovale*
Anthropometric indicators at birth (WHO)	**Weight**	4th percentile, (-1.73 z-score)	17th percentile, (-0.96 z-score)	7th percentile, (-1.47 z-score)	15th percentile, (-1.03z-score)	<1st percentile, (-2.95 z-score)
	Height	5th percentile, (-1.69 z-score)	52nd percentile, (0.06 z-score)	5th percentile, (-1.64 z-score)	27th percentile, (-0.62 z-score)	no data
	Head circumference	37th percentile, (-0.32 z-score)	no data	17th percentile, (-0.95 z-score)	37th percentile, (-0.32 z-score)	no data
	BMI	9th percentile, (-1.33 z-score)	6th percentile, (-1.55 z-score)	19th percentile, (-0.89 z-score)	15th percentile, (-1.05 z-score)	no data
Current Anthro-pometric Indicators (WHO)	**Weight**	27th percentile, (-0.47 z-score)	1st percentile, (-2.55 z-score)	<1st percentile, (-2.18 z-score)	9th percentile, (-1.34 z-score)	3rd percentile, (-1.85 z-score)

	Height	25th percentile, (-0.87 z-score)	22nd percentile, (-0.76 z-score)	<10th percentile, (-1.27 z-score)	19th percentile, (-0.88 z-score)	39th percentile, (-0.27 z-score)
	Head circumference (Hesse)	33rd percentile, (-0.45 z-score)	34th percentile, (-0.40 z-score)	44th percentile, (-0.14 z-score)	51st percentile, (-0.02 z-score)	5th percentile, (-1.64 z-score)
	BMI	44th percentile, (-0.17 z-score)	<1st percentile, (-3.30 z-score)	42nd percentile, (-0.19 z-score)	16th percentile, (-0.98 z-score)	<1st percentile, (-2.87 z-score)
Anthropometric indicators according to the adapted nomograms for WB	**Weight**	around the mean percentile of the normal weight-to-age chart	below the mean but above the lower limit of the percentile range of the normal weight-to-age chart	above the mean percentile of the normal weight-to-age chart	within the lower half of the of the normal range on weight-to-age chart between the mean and -2SD	within the lower half of the percentile range, between the mean of the weight-to-age chart and -2SD
	Height	around the mean percentile of the normal height-to-age chart	slightly above the mean percentile of the normal height-to-age chart	around the mean percentile of the normal height-to-age chart	around the mean percentile of the normal height-to-age chart	above the mean percentile of the normal height-to-age chart (between the mean and +2SD values)
	Head circum-ference (HC)	above the mean percentile of the normal HC-to-age chart	around the upper percentile range (+2SD) of the normal HC-to-age chart	slightly above the upper percentile range (+2SD) of the normal HC- to-age chart	within upper half of the percentile range (between the mean and +2SD values)	within upper half of the percentile range (between the mean and +2SD values)
Molecular genetic confirmation of the diagnosis		At the age of 2 years Screening for microdeletions	At the age of 4 years Screening for microdeletions	at 3 months Targeted analysis	at 4 months Targeted analysis	At the age of 3 yearsTargeted analysis
Phenotype		Typical for infants with WBS facial phenotype; synophrys; Dentition - 1st tooth at the age of 6 mos. diastema, microdontia	Typical for infants with WBS facial phenotype; bilateral epican- thus; Dentition - 1st tooth at 1 year + 7 months; diastema; microdontia	Typical for infants with WBS facial phenotype with a well distinguished stellar iris pattern; bilateral epicanthus; Dentition - absent	Typical for infants with WBS facial phenotype with a well distinguished stellar iris pattern; bilateral epicanthus; diastema, microdontia	Typical for infants with WBS with sparse stellar pattern of the iris, bilateral epicanthus, diastema, microdontia
Neurological and mental development		Started walking – at 20 months; Fine motor skills - impairment; Speech understands when talked to, has difficulties in formulating entire phrases.	Started walking – at 4 yrs. Fine motor skills impaired; Speech - understands and answers questions, but has difficulty formulating whole words and phrases; Muscular hypotonia, highly vivid reflexes;	Active back tummy rolling; actively crawls; tracks objects; grasps objects actively and steadily; makes baby sounds; Increased muscle tone of the limbs, brisk tendon reflexes up to clonus of the feet	Started walking – at 2 yrs., after rehabilitation; Speech - first words at 2-yrs., very advanced, formulates sentences, communicates verbally, recites, sings, works with a speech therapist; Fine motor skills - difficult; Very advanced development in all areas for WBS;	Started walking - at 16 mos. Fine motor skills - impaired; First words - at 2 yrs., intonation is age adjusted, well developed.

Cardiovascular system	CVS - no pathological findings; BP not measured	CVS - no pathological findings; BP not measured	CVS - pulmonary stenosis; mild valvular pulmonary stenosis and bifurcation stenosis; BP not measured	CVS - pulmonary stenosis improv- ing with age and SVAS; BP – not measured	CVS - foramen ovale (closed); BP - not measured
Gastrointestinal tract	No complaints	Feed difficulties - accepts only pureed foods, struggling with solids; Constipation	Feeding difficulties - rejects lumpy foods, eats slowly; frequent regur- gitation.	Feeding - requires more patience and time; the transition to some new foods takes longer.	Feeding difficulties in transition to solid foods in infancy, has trouble with textures such as fruits and purees, eats very well on biscuit-like foods. Tendency to constipation
Genitourinary system	A normal find	Cryptorchidism bilaterally; Ultrasound well differentiated pyra- mids, medullary nephrocalcinosis, unilateral hydronephrosis 1st degree	No data	Consistent follow- up; subtle bilateral nephrolithiasis	Primary nocturnal enuresis; normal findings on Ultrasound
Endocrine system; Calcium, Vitamin D, TSH	Calcium and phosphate homeosta- sis - normal; TSH – increased, with normal values of FT3/FT4 – monitored	Hypercalcemia, hypercalciuria; Clinical hypothyroidism Hypovitaminosis D	Calcium and phosphate homeostasis normal; TSH – normal.	Calcium and phosphate homeosta- sis - normal; TSH – normal. Hypovitaminosis D	Calcium and phosphate homeostasis - normal; TSH - no data. Hypovitaminosis D.
Connective tissue	Joint hypermobility	surgically repaired unilateral ingui- nal hernia; Joint hypermobility	Joint hypermobility	surgically repaired bilateral ingui- nal hernias and umbilical hernia; Joint hypermobility	surgically repaired umbilical hernia; Joint hypermobility
Vision and hearing	Hearing and vision not impaired, no medical data records available	Hearing and vision not impaired, no medical data records available	Hearing and vision not impaired, no medical data records available; hyperacusis	Vision - initial signs of myopia; hearing - not impaired; hyperacusis	Hearing and vision not impaired, no medical data records available; hyperacusis
Behavioral features	Loves music; Sleep difficulties; Hyperactivity	Loves music, plays with other children with pleasure; Previously sleep difficulties, resolved by still ongoing therapy: falls asleep more easily and sleeps through the night;	Sleep problems (difficulties in fall- ing asleep and sleeping through the night); Hyperactivity	Loves music; No sleep problems; very communicative and friendly; Hyperactivity; attention deficit	Loves music; Hyperactivity
Time since counseling	24 months	17 months	16 months	11 months	9 months

Outcomes after genetic counseling	Comprehensive parent education in WBS features and necessary followup schedule. Detailed plan for lifelong follow up for parents and pediatricians prepared.Individual growth charts for followup by the pediatrician prepared. Annual followup evaluation. Family further planning counseled.	Comprehensive parent education in WBS features and necessary followup schedule. Detailed plan for lifelong followup for parents and pediatricians prepared.Individual growth charts for follow-up by the pediatrician prepared.	Comprehensive parent education in WBS features and necessary followup schedule. Detailed plan for lifelong follow up for parents and pediatricians prepared. Individual growth-charts for followup by the pediatrician prepared.	Comprehensive parent education in WBS features and necessary follow up schedule. Detailed plan for lifelong follow up for parents and pediatricians prepared.Individual growth-charts for follow up by the pediatrician prepared. Parents are exclusively compliant to the schedule and present annual reports of all check-ups to the genetic counselor.	Comprehensive parent education in WBS features and necessary follow-up schedule.Detailed plan for lifelong follow-up for parents and pediatricians prepared.Individual growth-charts for follow-up by the pediatrician prepared.Family further planning counseled.
Encountered complications	Subclinical hypothyroidism and followup.	Severe hypothyroidism identified - immediate supplementation. Moderate hypercalcemia with hypercalciuria and nephrocalcinosisidentified dietary intervention; followup by nephrologist.	No	No	Severe dental problems and profound anxiety from doc-tors/dentists (anesthesia is discussed for treatment).
Intervention results	Physical therapy is very beneficial for development of motor skills. Despite intensive speech therapy beginning of speech and speech development were very delayed. Very good integration among children.	The family is skeptical about working with any specialist and prefers not to address the problem to teachers, despite the school offered special counseling. No further contact with our geneticist (living in another city).	Very early intervention by physical therapy with incredible effect and very advanced motor skills development basic milestones achieved within the normal (no WBS) range. No further contact with our geneticist (living in another country).	Very early intervention by physical therapy with incredible effect and very advanced motor skills development basic milestones achieved within the normal (no- WBS) range. Very early intervention and working continuously with a speech therapist. Speech is very well developed, rich; poems and songs reproduction is no problem. Very communicative, has no fear of doctors, very fast integration.	Early intervention by physical therapy with very good effect; very good motor skills development. Speech development is good, loves singing songs. Very good integration among children.

Psychological evaluation in all five children found moderate intellectual disability (generally corresponding to an IQ between 35 and 49). Motor development delay was present in all children, driving all families to start working with physical therapists. All children showed remarkable results due to this intervention, however, as expected in WBS fine motor skills remain continuously impaired. Speech development is delayed as well, with typically more simplified speech compared to peers in all verbal WBS children but also with significant patient-to-patient differences, to a great extend dependent on speech therapy interventions. All children are very friendly and smiling a lot; they are highly energetic and hyperactive; they respond verbally or emotionally when being spoken to, and adore music, which has a stress reducing effect on them.

Two families feared stigmatization by surrounding

people, including teachers and healthcare professional; they feel psychological and emotional pressure when they have to talk about the condition of their child, especially outside the family.

Family History

Negative family history for congenital conditions, intellectual disabilities, reproductive failure or consanguinity was found in four out of five families. Three first-trimester pregnancy losses (of the proband's grandmother) and a child with an intellectual disability (a child of the grandmother's sister) were reported for the maternal side in one family, but no diagnostic testing was done. Two children are firstborn in their families, and three have older siblings. Both partners were tested for the WBSmicrodeletion in one family, with negative result.

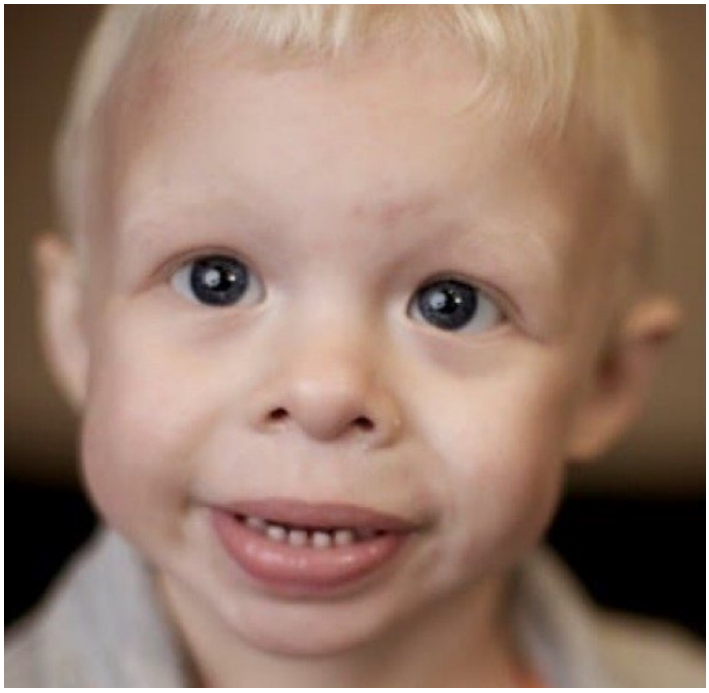

Figure 1: Characteristic facial features in Williams-Beuren syndrome (see text explanations). [13]

Discussion

Williams-Beuren Syndrome (WBS)

Clinical Characteristics

The Williams-Beuren syndrome (WBS) is a congenital genetic disorder with prevalence 1:7,500 - 1:20,000 worldwide, across all populations. It is a multisystem disease with variable clinical manifestation [10-12].

General Features

WBS individuals have very distinct **facial phenotype** observed from birth on and described historically as an "*Elfin facies*". Typical features are broad forehead, bitemporal skull narrowing and a dolichocephalic head configuration. The zygomatic bone is underdeveloped and flat, making the cheeks appear small and rounded. Periorbital swelling and thin eyebrows are common. Adults with WBS typically have characteristic long face and neck.

The eye color is often light, with irises having a characteristic stellar-like (lace-like) pattern (visible in light irises). Over half of the patients (>65%) have strabismus (most often esotropic) and about half of them may develop **hyperopia**. **Cataract development** is common with advancing age; a specific vascular pattern with more convoluted vessels may be present in the fundus; **amblyopia** and **impaired depth perception** might cause balance problems on uneven surfaces or stairs. Younger children often have **epicanthus**; obstructed nasolacrimal duct is observed more commonly.

The nose back is short, broad and flat, the tip is

rounded and the nostrils are often anteverted. The philtrum is high and flat, the vermilion is thicker, full and prominent; the mouth-opening is relatively wide. There is a pronounced micrognathia. **Teeth** are affected by malocclusion and diastema; microdontia and enamel hypoplasia are common.

The earlobes are larger, which becomes more prominent with age. Children more often develop **middle ear inflammation** and about 60% develop chronic otitis media. Excessive cerumen secretion is typical. Most patients (84-100%) develop **hyperacusis** with discomfort at sounds of at least 20 db lower than unaffected individuals; some patients have **phonophobia**, with slow tolerance development with aging. Paradoxically, individuals with Williams syndrome have an extraordinary affinity for music, they love to listen to music and dance; music often helps stress-reducing and attentionfocusing for longer time. About 63% of children and about 92% of adults develop progressive, usually mild to moderate **sensorineural deafness**, affecting especially the high frequencies range in adults. Vision and hearing problems require annual life-long ophthalmological and otorhinolaryngological follow-up [1,2,5,7,8,11,14,15].

Growth and Development

Growth delay and low weight are very common features of WBS, sometimes starting even during pregnancy with noticeable intrauterine growth retardation. To some extend growth problems result from feeding difficulties in infancy, motor delay incl. the fine motoric delay affecting the tongue muscles, the muscle hypotonia, joint hypermobility, etc. Children with WBS usually have weight, height and head circumference below the 75th percentile of the average range for their age. A major growth spurt occurs at the time of puberty, but altogether, WBS adults tend to be short in stature. For this reason, adapted growth charts for individuals with WBS were issued, for growth evaluation during childhood by pediatricians at each visit [1,2, 7-9,16].

Intellectual disability (DSM-5) is usually **mild** (IQ 50-69) **to moderate** (IQ 36-49) in 75% of cases. Conceptual skills (literacy, goal orientation, concept of numbers, money and time, etc.) are slightly to significantly more limited than in peers. Difficulty in acquiring academic knowledge is observed and a personalized approach in education is necessary. Social relationships are immature, social interpretation and understanding of hints is difficult, and communication is more direct; emotional controlling is difficult and tantrums are not uncommon. Adult WBS individuals are able to learn taking care of themselves and performing daily activities with adequate and intensive intervention [10,11].

Specific cognitive profile (which does not necessarily correlate with the IQ level) is observed in 90% of the cases and is characterized by impaired visual-spatial intelligence and abilities to manipulate numerical information, but well-developed short-term memory, as well as remarkable speech skills and an exceptional ability for remembering and recognizing faces in adulthood. Speech and language skills start developing later compared to other peers, but adults have unexpectedly good enunciation, auditory memory, and vocabulary, and often impress with their speech. Arithmetic skills are greatly affected throughout life. Basic motor skills develop slower, and fine motor skills remain impaired throughout life. The capacity for behavioral adaptive responses is severely affected at all ages. Attention deficit and hyperactivity are frequently observed [10,11,15,17,18].

Individuals with WBS are extremely **friendly**, full of empathy, love to be among other people and are usually preferred company; they are very emotional, easily frightened and often have **specific anxiety** [10,11]. Sleep problems (prolonged latency, reduced sleep efficiency) are common, perhaps caused by night-time melatonin absence or reduced peak [11,19,20].

Cardiovascular System

Cardiovascular disorders (in about 80% of the cases) are clinically the most significant group of symptoms, etiologically associated with the insufficient elastin synthesis. Reduced elastin amounts in the wall of the large arteries, results in stenosis. A supravalvular aortic stenosis (SVAS) is found in about 75% of patients. It may be of segmental "hourglass" type or may involve a greater span of the aortic wall, and sometimes requires surgical correction [1-3,7,8,21]. WBS patients require special considerations prior to any sedation and/or anesthesia (e.g. during surgery).

Individuals with biventricular outflow tract obstruction or otherwise at increased risk of myocardial insufficiency must be consulted by experienced cardiologist and anesthesiologist [22-25].

Peripheral pulmonary stenosis in childhood is often auscultated as a heart murmur; if more severe stenosis may cause fatigue and shortness of breath even without physical exertion. In the majority of the cases, it improves naturally with aging [1,2,7,8].

Arterial hypertension as a result of stenosis of renal arteries can be systemic, but it can also be asymmetric and restricted to a certain part of the body, as a result of narrowing of local arteries; thus, measured blood pressure values can vary over different blood vessels. For this reason, blood pressure of WBS patients should always be measured in at least three extremities. Arterial hypertension requires good control (by standard medications), especially in childhood when it is usually not expected and identified [1,2,7,8]. Other elastin-dependent arteriopathies (e.g. mesenteric) may cause local symptoms, such as abdominal pain.

The cardiovascular complications of elastin arteriopathy in WBS must be expected and followed-up regularly (Doppler echocardiography, ECG): every 3 months during the first year of life, at least once annually until 5 years of age and once every 2-3 years lifelong. Blood pressure values in 3 or all 4 extremities must be recorded at each pediatrician/physician visit or at least once a year throughout life. In adulthood surveillance includes searching for signs of: mitral valve prolaps, aortic valve insufficiency, hypertensive cardiomyopathy, hypertension, prolonged QT-interval, arterial stenoses, by means of Doppler echocardiography, ECG, or CT, MRI, catheterization if necessary [1,2,7,8,26].

Endocrine System and Microelements

Usually, mild idiopathic hypercalcemia and hypercalciuria develop in 15-45% of all WBS patients, requiring regular control. Serum calcium levels should be monitored every 4 months until 12 months of age, every 4-6 months from one to two years of age, and once in 2 years or as needed after this age and throughout life. Urine calcium levels and calcium/creatinine ratio testing (random spot or 24-hour urine) is recommended once a year. Clinical signs of hypercalcemia are irritability, vomiting, constipation, muscle cramps. The exact pathophysiological mechanism of the hypercalcemia in WBS is not fully understood, but to some extend it is related to the increased intestinal resorption of calcium and the susceptibility to hypervitaminosis D. First line management of hypercalcemia is controlled (but never fully restrictive) dietary intake (for example of dairies). Rarely, a drug therapy under cardiological monitoring might be necessary.

Excessive vitamin D levels are commonly found, however, hypovitaminosis D was prevalent among Bulgarian WBS patients. For this reason, plasma vitamin D levels should be monitored prior any correctional activities. By hypervitaminosis, avoiding common children food supplements with vitamin D and strong skin sun protection factor might be recommended [2,7,8].

WBS individuals are commonly born with hypoplastic thyroid gland and might develop clinical (in 5-10% of the cases) or subclinical (in ca. 30% of the cases) hypothyroidism. Clinical hypothyroidism causes further deterioration of the already compromised physical growth and intellectual development. Therefore, a lifelong monitoring of serum TSH and fT4/fT3 levels is essential for all patients [1,2,7,8].

Premature puberty (at 6-12 years) occurs in about 18% of cases. Therapeutic intervention is rarely necessary, but consultation with an endocrinologist might be necessary. Individuals of both sexes are fertile [1,2,7,8].

Diabetes mellitus and obesity are common in WBS adults, requiring beginning with serum glucose screening at a young age (between 13 and 20 years). Dietary control and regular daily activity are necessary [1,2,7,8].

Musculoskeletal and Nervous System

Muscle hypotonia in infancy and joint hypermobility cause compensatory posturing of the body, in order to maintain balance and are a co-factor in motor development delay. Adolescents and adults may develop peripheral muscle hypertonus and hyperreflexia [11]. Over time, an abnormal gait, spine deformities (kyphosis, scoliosis, lordosis), as well as joint contractures may develop [1,2,7,8].

Lifelong fine motor skill impairment causes object handling and writing difficult, and is also associated with solid food mouth processing, as tongue mobility is affected [1].

In rare cases, a Chiari type I anomaly (confirmed by brain magnetic resonance imaging) can be assessed, causing cerebellar symptoms such as ataxia, dysmetria, tremor, dysdiadochokinesis, etc. [11]. A consultation with a neurologist is also held once a year or at necessity [1,2,7,8].

Gastrointestinal System

Gastrointestinal disorders include breastfeeding and feeding difficulties in childhood. Constipation is very common and obstinate. Intermittent abdominal pain is very typical and might result from various processes, such as mesenteric artery stenosis; gastrointestinal reflux; hiatal hernia; peptic ulcer; cholelithiasis; diverticulitis; ischemic bowel disease; bowel-motility problems; rectal prolapse; hemorrhoids; intestinal perforation; it can also be psychogenic - out of fear [1,2,7,8].

Urinary System

About 50% of WBS patients develop renal artery stenosis, associated with arterial hypertension. About 10% have congenital genitourinary malformations. Bladder diverticula develop over time in about half of the cases, and nephrocalcinosis - in less than 5% [1,2,7,8]. Pollakiuria and enuresis are found in at least half of the children. Diurnal incontinence might last until the age of 4; nocturnal enuresis might continue by the age of 10 and ca. 3% of adults may still have it [1].

Connective Tissue

Common aberrant connective tissue findings are umbilical and inguinal herniations, susceptibility to diverticula of the bladder and the colon, and rectal prolapse. Joint hypermobility or contractures not rare. The voice is often shrill because of the insufficient elastin in the vocal cords, the skin is hyperextensible, lax and soft [1,2,7,8,11].

Recommendations for Surveillance and Follow-up of Children with WBS

Key efforts in surveillance of WBS patients are focused on follow-up, prevention, symptomatic treatment and interventions for supporting their speech, motor and intellectual developments. Useful ageadapted checklists of recommended clinical examinations, their regularity and suggestive findings are issued by the American Academy of Pediatrics and the Canadian Association for Williams Syndrome [2,16]. Furthermore, the Canadian Association provides adapted WBS growth charts for height, weight and head circumference in female and male patients [16]. A summary of these recommendations, adapted with minor changes from the American Academy of Pediatrics checklist, is presented in table 2. Recommendations include:

- Thorough physical examination and growth monitoring (height, weight, head circumference) at every physician visit until age of 5 and at least once annually lifelong.

- Cardiovascular assessment (echocardiography, ECG) at least once every 3 months up to 1 year of age, once annually until 5 years of age and once every 2-3 years thereafter (depending on the individual situation). Screening for hypertension and elastin-based arteriopathy of the aorta, the pulmonary arteries, the renal and some other large arteries in all ages, as well as for mitral prolapse, aortic valve insufficiency, hypertensive cardiomyopathy, prolonged QT-interval, and arterial stenoses. Blood pressure and heart frequency are registered at each physician visit over the first years and at least once annually lifelong. Blood pressure measurement should include minimum three, preferably all four extremities. Hypertension drug therapy follows standard protocols after renal artery stenosis is excluded.

- Cardiac surgery - surgical correction of severe supravalvular aortic stenosis, pulmonary artery stenosis, renal artery stenosis, mitral valve insufficiency might be necessary at an early age.

- Any surgical intervention or other procedure requiring sedation or anesthesia necessitates cautious cardiological and anesthesiologic evaluation prior to procedure, to avoid myocardial insufficiency due to ventricular artery obstructions.

- Serum calcium levels evaluation every 4 months for the first year of life, every 4-6 months from 1 to 2 years

of age and once every 2 years for life (or as necessary). Urine calcium levels evaluation (screening for hypercalciuria) and urine calcium/creatinine ratio (random spot or 24-hour) once a year. Vitamin D levels are commonly impaired and should also be regularly monitored.

- Screening for hypothyroidism trough TSH serum level monitoring (together with FT3 and FT4 or subsequently) should be done once annually up to 3 years of age and every 2 years thereafter lifelong.

- Ophthalmological evaluation for visual impairment or other problems (e.g. strabismus) should be done once annually; WBS adults are predisposed to early cataracts. Obstruction of the lacrimal ducts is a common finding.

- Otorhinolaryngological evaluation with audiogram for early identification of sensorineural hearing impairment is recommended once annually up to 30 years, and once in 5 years thereafter. Common findings are otitis media and excessive cerumen secretion. Some patients need antiphones to cope with their hyperacusis.

- A single ultrasound screening by nephrologist for kidney and bladder malformations, and renal artery stenosis is recommended. Further follow-up in children is at the discretion of the specialist and in adults Doppler US should be done once every 10 years. Annual basic urine screening and evaluation of urine calcium/creatinine ratio, as well as serum urea (BUN) and creatinine levels are helpful for early detection of nephrocalcinosis and kidney functional impairment. Recurrent urinary infections are more common (in about 30% of cases).

- Constipation is a very common problem (associated with muscle hypotonia, hypercalcemia, etc.) and must be addressed regularly and intensively by the parents. Gastro-esophageal reflux disease (GERD) is common and important for the differential diagnosis of abdominal pain, which can be also resulting from, hiatal hernia, peptic ulcer, cholelithiasis, diverticulitis, ischemic bowel disease, mesenteric arteries stenosis but also psychogenic (anxiety, panic attacks). Feeding problems are very common, especially the dislike of new or solid foods or foods with certain textures. They can be overcome very slowly, with great parental patience and sometimes with support from a speech therapist.

- Annual evaluation for herniations.

- Annual orthopedic assessment for contractures, spine deformities (kyphosis, scoliosis, lordosis).

- Neurological assessment is recommended in case of recurrent headaches, dysphagia, ataxia, feeling of dizziness and weakness, to exclude Chiari I malformation (by MRI); annual basic neurological evaluation of muscle tonus might be discussed.

- WBS patients are predisposed to diabetes and obesity. Therefore, a balanced diet and exercises are essential for their health. Screening for glucose intolerance and hyperglycemia by serum glucose levels and oral glucose tolerance test (OGTT) starts annually before 20 years of age.

- Puberty might begin earlier, however rarely precautious and usually no medical therapy is necessary; WBS individuals are fertile and have 50% chance of having an affected child.

- Regular dental evaluation and care are recommended, however most of the patients have fear of these examinations especially in childhood; this may prompt treatment under sedation.

- Further family planning is important part of the genetic counselling and should elucidate all details about recurrency risks and options for preimplantation and prenatal testing in future pregnancy.

- Working with different specialists is very helpful for the WBS patients and their families. It requires patience and special approach. Studies demonstrate that early and regular intervention programs are very helpful in speech and motor development, with remarkable results into adulthood. Training programs for schooling in daily living and independency to some extend are very beneficial. Working with psychologist and/or psychiatrist helps coping with anxiety, panic attacks, fears, sleep disturbances or hyperactivity. Due to the significant contrast between the level of development in different cognitive areas (e.g., very good verbal and nonverbal reasoning, but impaired spatial understanding), general tests (such as the Wechsler Intelligence Scale for Children) are not appropriate for assessing the intellectual impairment, and rather tests for independent assessment of

the cognitive domains (such as the Differential Ability Scales II) are recommended [27].

Contact of families with other WBS-families and patient groups is very beneficial.

Table 2: Summary of WBS clinical features and recommendations for follow-up of patients with Williams-Beuren syndrome at different ages, as recommended by the American Academy of Pediatrics [2,7,16].

Affected organ or body system: Symptoms for following-up	**Early childhood**	**Child hood**	**Adult hood**	**Frequency %**	**RECOMMENDATIONS**
Thorough physical examination	**Yes**	**Yes**	**Yes**	NA	At each physician visit or at least once annually. Ensure that the growth delay is not drastic, take measures as necessary Anesthesia counseling and specialist evaluation before any operation, sedation, etc
CAUTION by SEDATION or ANESTHESIA!!!	**Yes**	**Yes**	**Yes**		
Vision:					Ophthalmological examination lifelong once annually for any vision problems and for strabismus for all ages Adults are also monitored for early cataractsall ages.
Strabismus (esotropia)	Yes	-	-	50	
Hyperopia (hypermetropia)	-	Yes	Yes	50	
Cataract	-	-	Yes	-	
Otorhinolaryngology:					Otorhinolaryngology examination and audiogram, lifelong once annually. Cerumen special care. **Antiphons (if necessary).**
Recurrent otitis media; chronic otitis media	Yes	Yes	-	50	
Progressive sensorineural hearing loss	-	Yes	Yes	65	
Hypersensitivity to sounds	Yes	Yes	Yes	90	
Dental status:					Regular dental examinations and professional dental cleaning every 6 months up to 12 years of age; every 4 months after 12 years of age (anxiety is common). Orthodontal examination/counseling for malocclusion after 6-8 years of age
Enamel hypoplasia	Yes	Yes	Yes	95	
Microdontia, Diastema	Yes	-	-		

Malocclusion	-	Yes	Yes	85	
Cardiovascular problems:					Basic examination at each physician visit for elevated blood pressure (of 3 or 4 extremities), heartfrequency, heart tones. Once annually, lifelong: electrocardiogram (ECG). At least once annually for age 1 to 5 years and once in every 2 years thereafter (or as necessary): thorough examination by a cardiologist with blood pressure measurement on 3 or 4 extremities,echocardiography, Doppler sonography (for severe stenosis incl. CT, MRI, catheterization), ECG.
Basic examination	Yes	Yes	Yes	80	
Supravalvular aortic stenosis	Yes	Yes	Yes	75	
Supravalvular pulmonic stenosis	Yes	Yes	Yes	25	
Peripheral pulmonic stenosis (PPS)	Yes	-	-	50	
Stenoses of other arteries	-	Yes	Yes	20	
Ventricular septal defect (VSD)	Yes	-	-	10	
Arterial hypertension	-	Yes	Yes	50	
Prolonged QT interval	-	Yes	Yes	13	
Genitourinary problems:					Screening at diagnosis - single ultrasonographic (US) examination (Doppler) of the kidneys and renalarteries; US evaluation for nephrocalcinosis; for bladder malformations, diverticula. In adults - USexamination once every 10 years. Annually lifelong: serum BUN (serum urea) and urinalysis; serum creatinine - as necessary.In case of complications (persistent hypercalcemia, hypercalciuria, nephrocalcinosis) - consultationwith nephrologist.
Malformations	Yes	Yes	Yes	5	
Enuresis (diurnal, nocturnal)	/	Yes	-	50	
Nephrocalcinosis	Yes	Yes	Yes	<5	
Bladder diverticulosis	-	Yes	Yes	50	

Gastrointestinal problems:					Continuous prevention of constipation. Each situation of abdominal pain should be addressed critically and having in mind that abdominal pain may be due to mesenteric artery stenosis(!) but alsoreflux, hiatal hernia, peptic ulcer, cholelithiasis, diverticulitis, ischemic bowel disease (due to motilityproblems, rectal prolapse, hemorrhoids, bowel perforation), and quite common - psychogenic (out offear).
Feeding difficulties	Yes	Yes	-	70	
Constipation	Yes	Yes	Yes	50	
Diverticula of the colon	-	Yes	Yes	30	
Prolapse of the rectum	Yes	Yes	-	10	
Skin and soft tissues:					At least once annually, lifelong: surgical examination for hernias; At least once annually: check-up for joint contractures, spinal deformities, gait problems.
Soft and hyperelastic skin	Yes	Yes	Yes	90	
Inguinal hernia	Yes	-	-	40	
Umbilical hernia	Yes	-	-	50	
Premature greying of hair	-	-	Yes	90	
Musculoskeletal problems:					At least once annually, lifelong: orthopedic examination for joint hypermobility, contractures, scoliosis, kyphosis, lordosis. Daily movement and exercise. Physical therapy and working with specialist on a regular basis arehighly recommended.
Joint hypermobility	Yes	Yes	-	90	
Joint contractures	Yes	Yes	Yes	50	
Radio-Ulnar Synostosis	Yes	Yes	Yes	20	
Kyphosis	-	-	Yes	20	
Scoliosis	-	Yes	Yes	18	
Lordosis	-	Yes	Yes	40	
Pathological gait	-	Yes	Yes	60	

Calcium homeostasis and vitamin D:					Serum calcium levels: once every 4 months up to 2 years of age, once every 2 years thereafter (urinelevels only if necessary). Consultation on nutrition and dietary calcium intake; dietary calcium corrections are made only under physician supervision and never by parents alone! Control of serum vitamin D levels. Control of vitamin D supplementary intake and caution for sunprotection too! Changes should be made at the discretion of a pediatrician.
Hypercalcemia	Yes	-	Yes	15-45	
Hypercalciuria	Yes	Yes	Yes	30	
Vitamin D hypervitaminosis	-	-	-	-	
Endocrine problems:					Strict follow-up of TSH levels (±FT3, FT4) once annually up to 3 years of age; thereafter once in 12to 24 months lifelong (no TAT and MAT measurement necessary - the hypothyroidism is caused bygland hypo-/aplasia). In case of puberty signs at 6-12 years - counseling by endocrinologist. From the age of 13 years annual diabetes screening (serum glucose; tolerance test)
Hypothyroidism	Yes	Yes	Yes	5-10	
Early (but not precocious) puberty	-	Yes	Yes	20	
Diabetes mellitus	-	-	Yes	15	
Obesity	-	Yes	Yes	30	
Neurological problems:					Thorough neurological examination once annually for signs of muscle hypotension, hypertension,cerebellar symptoms. Head MRI if Chiari is suspected.
Hyperactive tendon reflexes	-	Yes	Yes	75	
Chiari type I malformation (caudal retraction of the cerebellar tonsils through the foramen magnum)	Yes	Yes	Yes	10	
Central muscular hypotension	-	Yes	-	80	

Peripheral muscular hypertension	Yes	Yes	Yes	50	
Cognitive and developmental problems:					Physical monitoring according to the age-adapted WBS nomograms for height, weight and head circumference at each visit by physician up to 5 years of age and once annually thereafter until adolescence. Early intervention programs to support motor and language development, working with specialists(e.g. speech therapist, physical therapist), adapted schooling and learning programs, nutritional therapy if necessary
Motor and physical developmental delay	Yes	Yes	-	95	
Intellectual impairment (normal intelligence in up to 5%)	-	Yes	Yes	75	
Visuospatial cognitive impairment	-	Yes	Yes	95	
Behavioral features:					Evaluation by psychologist/psychiatrist, symptomatic therapy if necessary (fear, depression, hyperactivity). Training in social skills.
Attention Deficit Hyperactivity Disorder (ADHD)	-	Yes	-	65	
Anxiety disorder (specific phobias, generalized anxiety)	-	Yes	Yes	70	
Sleep disorders	-	Yes	Yes	65	

NA - not applicable

Inheritance

In most cases, Williams syndrome occurs *de novo*, i.e., the deletion is due to a random spontaneous (newly) occurring event in the formation of one of the gametes of one parent. In case the parents have a normal phenotype, corresponding to absence of a germline deletion, the probability of having a subsequent affected child is low, but the risk is slightly higher than the population risk, tending towards 1%. The reason may be one of the following: **gonadal mosaicism in the parent** (there are a few rare familial cases of Williams syndrome described, with more than one child with the syndrome in a family of clinically healthy parents) in which case the recurrence risk cannot be evaluated; presence of asymptomatic carrier of an inversion polymorphism on chromosome 7 in one parent, occurring in 25% of parents of children with WBS, but in only 6% of individuals in the general population, with a recurrence risk estimated at 1:1750. Therefore, it is recommended, when planning a subsequent pregnancy, the proband's parents to consider prenatal or preimplantation diagnosis. Siblings of individuals with WBS in parents with inversion may also anticipate such a diagnosis in family planning.

Individuals with WBS of both sexes are fertile and can transmit the deletion to their offsprings with a probability of 50% for each pregnancy, which requires either controlled contraception or prenatal diagnosis planning [1,4,27-32].

Molecular genetic features

WBS is a common microdeletion syndrome, caused by loss of 1.55 Mb (mega bases) in the long arm of chromosome 7 (at locus 7q11.23) in over 90% of the cases. In the remaining up to 10% of cases it is 1.84 Mb in size. It results in haploinsufficiency of 26 to 28 genes, associated with the typical clinical manifestations of the condition - *a contiguous genes syndrome*. Rarely, the deletion may be larger, inevitably causing more severe clinical presentation. The WBS deletion always includes the elastin gene [1,11,28,29]. "Golden standard" in molecular genetic testing for WBS testing is fluorescent in situ hybridization (FISH) with 7q11.23-specific probes. Currently, other CNV-detection techniques, such as multiplex ligation-dependent probe amplification (MLPA) and array-based technologies, are regularly used, especially by broader clinical differential diagnosis [1].

Future Directions

With increasing clinical recognition of the WBS and publishing of more clinical and other information on the condition, interest on WBS research is growing. Efforts are made to clarify the exact role of each of the deleted 26 (28) genes in the syndrome pathogenesis and especially in the neurodevelopment; to understand the causes and the features of the specific cognition profile and anxiety disorders in WBS; to understand the pathogenesis of cardiovascular, neurological and other pathogenic findings in WBS-patients (more information can be found for example at the *Williams Syndrome* Association internet page).

Conclusion

Even though there is no etiological treatment for WBS, efforts should be focused on follow-up, prevention, symptomatic treatment and early interventions, in order to support motor, speech and intellectual development [1-3,7,8,26,30]. As described, WBS patients require lifelong regular medical surveillance from health care professionals with various medical background. In childhood, being cared for by their parents and followed-up by pediatricians, which are relatively familiar with the condition, in most European countries the WBS patients usually receive adequate surveillance. However, after 18 years of age, WBS patients cannot be followed-up by their pediatricians anymore; general practitioners and physicians are usually unaware of WBS and some patients naturally lose their parents. Several problems can occur at this point, regarding: the transition into adulthood-healthcare system; the assignment of a social worker who is responsible for the well-being of the patient and of a health care coordinator; the lack of specialized healthcare institution for evaluation and follow-up of patients with rare disorders; the necessity of a general practitioner that is aware of the conditions and its possible complications [1,2,7,8,26]. The above-described clinical cases reveal some weak sides of our social and healthcare system regarding patients with rare and chronic conditions, for example:

1. Insufficient state policy regarding genetic testing and genetic counselling, illustrated by the negligeable legal basis - only a small section of the Bulgarian Health Act devotes to clinical genetic testing. By comparison, the Genetic Diagnosis Act in Germany (GenDG), adopted in 2010, regulates all aspects of human genetics in detail, describes the obligations of healthcare providers to the patients, and establishes an independent interdisciplinary commission for genetic diagnosis (GEKO), which has so far defined eleven guidelines for medical genetic diagnosis, in compliance with the current level of scientific and medical development. The need to update and adopt an adequate legislative framework in our country emerges in our every-day--work as medical geneticists.

2. Negligible opportunities for the genetic professionals: to be the driver of an initiative to change the legislation; to be the initiator of the preparation and approval of national standards, guidelines and regulations for genetic testing and counseling; to be supported and acknowledged by official institutions as professional organization that is appointed and responsible to raise the awareness among healthcare providers with different background about the

benefits and indications for genetic counselling and testing.

3. Negligible opportunities for covering of the expenses for genetic testing, counselling and intervention programs by the only health insurance fund in the country. For most affected families this is the main reason for abstaining from referral to geneticist. This on the other hand results in lack of prevention and missed therapeutic opportunities.

4. Lack of any specialized healthcare center with a multidisciplinary team, where patients with complex genetic and other rare disorders can receive a coordinated surveillance and management for a variety of medical problems.

5. The lack of national genetic standards, state policy and information, makes most healthcare professionals and affected families unaware of the benefits of genetic counselling and testing.

6. There are almost no state-supported intervention programs for people with speech, motor or intellectual deficiency (most are private), nor any guidelines for establishing the most optimal strategy for improving the health status of patients [2,7].

Our efforts as genetic counselors are to help patients and their families understand the complex nature of genetic disorders, to support them in accepting the situation and to prepare sufficient information about expected future development. During genetic counselling, we have the opportunity to spend long time with the patients and their families and to get familiar with their greatest fears. We are the professionals, responsible to provide current knowledge and recommendations r the follow-up, surveillance and management of patients with rare genetic conditions. Knowing what to expect enables the physician to make informed clinical decisions.

An Informed Consent

We acknowledge the children with Williams-Beuren syndrome and their devoted parents, brothers and sisters, for their support and trust! Anonymized publication of the data in this article was agreed to and authorized by the parents of children with Williams syndrome consulted in our practice.

Glossary

Amblyopia - "lazy eye"; a neurological problem in which the brain does not correctly perceive and process the image received from one eye, and as a result it is excluded from the vision process.

Anteverted nostrils – the nostrils are oriented forward instead of mostly downward.

Vermilion – the red part of the lips; divided into upper and lower vermilion.

Esotropia - convergent strabismus, with the gaze of both eyes deviated towards the nose.

Epicanthus – the upper eyelid skin fold that covers the inner ocular corner.

Diastema – greater distance between teeth

Dolichocephalic configuration – longer anterior--posterior size of the skull, relative to its width.

Malocclusion - an incorrect arrangement of teeth that are not lined up.

Micrognathia – smaller mandible bone.

Microdontia - smaller teeth.

Proband – the patient who is the focus of genetic counseling.

OGTT – oral glucose tolerance test

WBS – William-Beuren syndrome.

Strabismus - squint.

Philtrum - the relief groove between the nose and the upper lip.

Phonophobia – fear of certain sounds.

Hyperacusis - increased sound sensitivity with re-

duced noise tolerance.

Cerumen - earwax.

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