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Clinical and neuropsychiatric status in children with Williams-Beuren Syndrome in Upper Egypt

Khaled Saad [a,*], Ahmed A. Abdelrahman [b], Alameldin M. Abdallah [a], Hisham A.K. Othman [c], Reda Badry [b]

[a] Department of Pediatrics, Assiut University, Assiut 71516, Egypt
[b] Department of Neurology & Psychiatry, Assiut University, Assiut 71516, Egypt
[c] Department of Clinical Pathology, Cytogenetic Unit, Assiut University, Assiut 71516, Egypt

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ABSTRACT

The aim of this study was to evaluate and explore the clinical, neuropsychiatric status and EEG pattern in a series of children with Williams-Beuren syndrome (WBS) in Assiut, Upper Egypt. We aimed to provide a comprehensive data comparable to what has been published, to enable us to make comparisons across different cultural areas. This will contribute to a better definition of the neuropsychiatric features that may be specific to WBS that allows early and better detection and management of those children.

Materials and methods: A series of 17 WBS children patients who consulted at our hospital were evaluated. The patients were assessed mainly for clinical, neurological, psychiatric and EEG status. We performed FISH for all patients.

Results: All patients had a deletion of the long arm of chromosome 7 (7q 11.23). All had elfin facies. Neurological examination revealed hypotonia in 25% of patients and rigidity (12.50%), brisk deep tendon reflexes (25%), abnormal plantar response (12.50%). Cerebellar and extrapyramidal signs were frequent: dysmetria (31.25%), dysdiadochokinesia (31.25%) and ataxia (18.75%). Epileptic seizures were present in 31.25% of patients and ADHD (37.5%). Autism was present in one patient. EEG abnormalities were present in 31.25%. Congenital cardiopathies were present in 62.50%.

Conclusion: Our data showed that WBS children had multi-systemic clinical complications and the management of those patients requires the pediatrician to understand the natural course of this condition, awareness of potential medical problems, and periodic baseline clinical, neuropsychiatric evaluations, monitoring, and rapid intervention to improve the medical care for patients who have WBS.

1. Introduction

Williams-Beuren syndrome (WBS) is a congenital developmental disorder caused by a hemizygous contiguous gene deletion on chromosome 7q 11.23. The deletion sizes range from 1.5 to 1.8 mega base pairs (Mb), encompassing the elastin gene (Weng et al., 2012; Barbara, 2010; Schubert, 2009). It occurs in approximately 1 in 7500 to 20,000 people (Schubert, 2009). Genetic diagnosis using fluorescence in situ hybridization (FISH) to demonstrate deletion of the WBS chromosomal region is the mainstay of laboratory diagnosis. The diagnosis can also be established by microsatellite marker analysis, multiplex ligation dependent probe amplification, quantitative polymerase chain reaction assay, or array comparative genomic hybridization (Barbara, 2010). Clinically, patients present with multiple systemic disorders including dysmorphic "elfin-like" facial features (wide mouth with full cheeks and full lips and periorbital fullness with a broad forehead). Gross developmental delays, poor physical co-ordination, and connective tissue abnormalities such as overly loose joints are obvious. Elastin arteriopathy occurs in 75% of patients with this syndrome. Any artery may be narrowed, and peripheral pulmonary stenosis (PPS) is common in early infancy. Supravalvular aortic stenosis (SVAS) is the most common arteriopathy requiring surgical correction (Weng et al., 2012; Barbara, 2010; Schubert, 2009). WBS children are at risk for systemic hypertension, with a frequency ranging from 5 to 70%. The etiology is found in only a small percentage of patients including renal artery stenosis and/or diffuse aortic

Abbreviations: CARS, Childhood Autism Rating Scale; EEG, electroencephalogram; FISH, fluorescence in situ hybridization; FSIQ, Full Scale IQ; GTC, generalized tonic clonic; PPS, peripheral pulmonary stenosis; SVAS, supravalvular aortic stenosis; WBS, Williams-Beuren syndrome; VSD, ventricular septal defect.

* Corresponding author at: Department of Pediatrics, Faculty of Medicine, University of Assiut, Assiut 71516, Egypt. Tel.: +20 100 608 0182; fax: +20 88 236 8371.
E-mail addresses: ksaad8@yahoo.com, ksaad8@gmail.com (K. Saad).

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narrowing and/or aortic coarctation. The vascular lesions in WBS seem to be linked to the reduced elastin synthesis and increased proliferation of vascular smooth muscle cells, but the exact pathways connecting the elastin deficiency to increased vascular cell proliferation are still unknown. WBS is associated with some endocrine abnormalities including, calcium, glucose and thyroid abnormalities. The frequency of occurrence of hypercalcemia is not known, as it is most often asymptomatic. Early onset hypothyroidism has been reported in children with WBS, though the most common thyroid abnormality observed is clinical or subclinical hypothyroidism. Diabetes mellitus has also been reported in adults with WBS (Barbara, 2010; Schubert, 2009; Bouchireb et al., 2010).

Generally, patients with WBS present with a mild to moderate intellectual disability, but normal intelligence has been documented in a small subset of individuals (Weng et al., 2012; Barbara, 2010; Schubert, 2009). The neurocognitive profile of WBS is characterized by severe visuospatial and visuoconstructive deficits in the context of relatively preserved face processing and language skills. Patients with WBS typically show hypersociability with a lack of inhibition and non-socially determined anxiety. Neurological features such as coordination difficulties, balance instability, hyperreflexia, choreiform and dystonic movements, extrapyramidal signs and oculomotor signs (nystagmus) have been described (Bellugi et al., 2000a; Tavano et al., 2010; Gagliardi et al., 2007).

2. Aim of work

The aim of this study was to evaluate and explore the clinical, neuropsychiatric status and EEG pattern in a series of children with Williams-Beuren syndrome (WBS) in Assiut, Upper Egypt. We aimed to provide a comprehensive data comparable to what has been published, to enable us to make comparisons across different cultural areas. This will contribute to a better definition of the neuropsychiatric features that may be specific to WBS that allows early and better detection and management of those children.

3. Materials and methods

17 children with WBS from 5 governorates in Upper Egypt have been diagnosed and followed at Assiut University Hospitals, Assiut University, Egypt; from December 2009 until December 2012. One patient excluded due to significant head injury and his parents refused to be included in our study.

Informed written consent was obtained from each caregiver. The study was approved by the Ethical Committee of Assiut University, Assiut, Egypt. The study was conducted on 16 patients. Investigated cases evaluated according to the following (Table 1):

1. Detailed history with carefully gathered information from the structured parent interview, paying special attention to family history of consanguinity, similar conditions of WBS in the family, autistic symptoms, social/interpersonal activities, self-care, pattern of any cognitive decline, behavioral and learning disorders, delayed motor milestones, intellectual disability, seizures and prenatal and perinatal history.
2. General and meticulous neurological examination: consisting of anthropometric measurements, blood pressure, cranial nerves examination, motor and sensory functions, gait, extrapyramidal signs and tests for cerebellar function.
3. Full Scale IQ (FSIQ) test: by applying Stanford Binet Intelligence Scale, Fourth Edition; the test is valid by using factorial validity, criterion validity and also some studies operate in the culture of Egypt that sub testes of Stanford-Binet (4th edition) (Melika, 1998).
4. For evaluation of autistic disorder, all patients were evaluated according to DSM-IV-TR criteria (American Psychiatric Association, 1994). Structured interviews of at least one hour each with both parents and child were conducted, in a room equipped with play material appropriate for age level. Later on, another two hour-session was conducted for classification of autism cases by using the Childhood Autism Rating Scale (CARS) (Schopler et al., 1994). CARS is a well-established scale for the screening and diagnosis of childhood autism with complete agreement between DSM-IV and CARS (Rellini et al., 2004).
5. The diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD) was based on DSM-IV-TR criteria for ADHD (American Psychiatric Association, 2000). Data about the children were collected through structured interviews, both with teachers and caregivers. The interviews included all possible symptoms related to ADHD. Each item scored yes if the symptom was endorsed as definitely present or no if the respondent indicated either sometimes, rarely or never. Based on DSM-IV-TR criteria, children diagnosed with ADHD were further classified into its hyperactive-impulsive, combined and inattentive types.
6. EEG was carried out in all patients in a calm dark room, in cooperative awake children; hyperventilation was used as a provocative test, in those who are uncooperative; sleep was induced with chloral hydrate or occasionally children were in natural sleep. All were done by the use of 10 channels conventional EEG Nihon-Khoden Japanese machine. The paper speed was 30 mm/s, with the use of "unipolar" as well as "bipolar" montages in the same record.
7. Fluorescence in situ hybridization (FISH): The diagnosis of WBS was confirmed using the FISH test. This technique enables the determination of a specific deoxyribonucleic acid (DNA) sequence in a chromosome band. The technique involves the hybridization of a fluorescent-labeled probe to its complementary DNA segment within a metaphase chromosome. The probe is visualized with fluorescence in the FISH technique. In our study, the hemizygosity for the elastin gene was analyzed using the LSI Williams syndrome region DNA probe (VYSIS®), according to Pinkle et al. (1986). This is a specific-locus probe marked with Spectrum Orange TM dye, which contains the locus of the ELN, the locus of the LIMK1 gene, and the locus of D7S613, a marker of chromosome 7. The control probe marked with Spectrum Green TM is included in the mixture and corresponds to loci D7S486 and D7S522 located in the 7q31 band. The presence of only 1 red signal (elastin gene) and 2 fluorescent green signals (markers of chromosome 7) indicates deletion of the elastin gene in one of the chromatids of chromosome 7, confirming the WBS diagnosis. In this case, the patient is considered FISH positive (Fig. 1). The individual who has 2 red signals (presence of the elastin gene in both chromatids of chromosome 7), and 2 green signals is considered FISH negative.
8. MRI brain: Brain MRI was done for all cases using MRI machine 1.5 T at MRI unit; Assiut university hospitals with the following protocol: (1) *Axial Diffusion weighted imaging (DWI)*; (TE):

Table 1
Summary of procedures used in the study.

Item	Procedures
Diagnosis of WBS	FISH and clinical assessment
Cardiovascular assessment	Echocardiography and blood pressure monitoring
Growth and development	Anthropometric measurements
Neurological assessment	MRI brain and neurological examination
Full Scale IQ test	Stanford Binet Intelligence Scale
Epilepsy	EEG and clinical assessment
Autistic disorder	DSM-IV-TR criteria and CARS
ADHD	DSM-IV-TR criteria for ADHD
Calcium status	Serum calcium

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