RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Clinical Follow-Up of Young Adults Affected by Williams Syndrome: Experience of 45 Italian Patients

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Received 25 February 2009; Accepted 18 August 2010

Williams–Beuren syndrome (WBS) is a multisystem disorder that requires ongoing management by a primary care physician familiar with the natural history and specific medical problems associated with the condition. While the natural history of the disease during infancy is well known, data about the adult WBS population have been published only in the last few years, and show a wide range of medical, neurological, and psychiatric problems. We investigated 45 young adult WBS patients (mean age 23 years, range 17–39 years) using a well-coordinated team which included a cardiologist, a nephrologist, an ophthalmologist, an endocrinologist, a gastroenterologist, orthodontist, and orthopedist. Here we describe the clinical features and medical complications in this cohort of patients. Most patients demonstrated a high frequency of multiple organ systems complications, in particular, abnormal body habitus; cardiovascular disease, and hypertension; sensorineural hearing loss; gastrointestinal symptoms including diverticular disease and abnormal glucose tolerance. We offer some suggestions for clinical monitoring which we propose will be useful in the overall care of adults with WBS. © 2011 Wiley-Liss, Inc.

Key words: *ELN* gene; management adult patients; rare disease; Williams–Beuren syndrome

How to Cite this Article:
Bedeschi MF, Bianchi V, Colli AM, Natacci F, Cereda A, Milani D, Maitz S, Lalatta F, Selicorni A. 2011. Clinical follow-up of young adults affected by Williams syndrome: Experience of 45 Italian patients.
Am J Med Genet Part A 155:353–359.

INTRODUCTION

Williams–Beuren syndrome (WBS; OMIM 194050) is a rare, multisystemic genomic disorder with a prevalence ranging from 1/7,500 to 1/20,000 [Morris et al., 1998; Stromme et al., 2002]. This syndrome is caused by a recurrent deletion of 1.55 Mb of the q11.23 region on chromosome 7 that involves the elastin gene.

The clinical phenotype is widely heterogeneous. During infancy and childhood the main clinical features include characteristic facial dysmorphisms, growth delay, intellectual disability with typical neurobehavioral profile and cardiovascular anomalies, most often supravalvular aortic stenosis (SVAS) and/or peripheral pulmonary stenosis. Various medical complications, such as arterial hypertension, subclinical hypothyroidism, celiac disease, and orthopedic problems, have also been described.

While the natural history of the disease during infancy and childhood is well known, descriptions of the adult WBS population have been published only in recent years [Pober and Morris, 2007]. These have revealed a wide range of medical, neurological, and psychiatric problems. As in children with WBS, the most common cardiac lesions observed in adults were SVAS and other vascular stenoses [Eronen et al., 2002]. Hypertension, a common feature in the general adult population, is even more frequent in individuals with WBS, but some studies showed no evidence of an age effect in cohorts comprising individuals 1–23 years of age and 11–44 years of age [Wessel et al., 1997; Broder et al., 1999]. Half of the adult patients with WBS have chronic constipation while a diverticular disease of the sigmoid colon was noted in about 11% [Partsch et al., 2005]. With respect to endocrinological abnormalities, Cherniske et al. [2004] described a cohort of WBS adults over 30 years of age, where 75% of them met the diagnostic criteria for either diabetes or pre-diabetes. The frequency and uniqueness of medical problems

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Published online 11 January 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.33819

found in adults with WBS suggest the need for continuing high-quality clinical management and medical care.

Here we report on the clinical analysis of a group of 45 Italian adolescent and young adult patients (22 females and 23 males).

STUDY POPULATION

Patients were recruited from the Department of Paediatrics and from the Medical Genetics Unit, at IRCSS Foundation Ospedale Maggiore Ca' Granda of Milan. In each patient diagnosis was confirmed by the typical elastin gene hemizygosity shown by FISH. None of the parents had clinical features of WBS suggesting that all cases were de novo presentations. One set of monozygotic twins was included in the study. Medical histories were obtained by direct interview with subjects, parents and caregivers, and patients entered a multidisciplinary follow-up protocol that had the specific purpose of detecting major medical complications connected to the syndrome. All WBS subjects underwent a thorough physical examination (including growth parameters plotted on WBS growth charts) followed by a series of clinical evaluations, as reported in Table I. For each patient body mass index (BMI) was calculated and subjects were accordingly classified into one of the following subgroups: <20 underweight, 20–25 normal weight, 25–30 overweight, and >30 obese.

Concerning neuropsychological and social data systematic evaluation of cognitive abilities among young adults affected by WBS was not one of the major aims of this study. Nonetheless we collected data about IQ scores, school and working situation, and living conditions for most of our patients (38 out of 45; 84%) through a questionnaire administered to parents or caregivers.

The intelligence quotient had been assessed in 28 patients out 38 (74%). In 14 cases the Wechsler Adult Intelligence Scale—Revised (WAIS-R) was employed, in seven the Stanford-Binet Scale, in three the Wechsler Intelligence Scale for Children—Revised (WISC-R). Griffiths Mental Development Scale and the Terman–Merrill Abbreviated Scale were used in one patient each.

Patients and their parents or caregivers gave their informed consent to participate in the study.

RESULTS

General Findings

Mean age at the time of study was 23.6 years (range 17–44 years). Mean age at the time of clinical diagnosis was 8.5 years (range birth to 32 years). These patients have been followed for a mean time of 6.7 years (range 1–14 years).

Five patients had a positive family history for genetic disorders, two for Down syndrome and three for mental delay of unknown etiology.

At the last clinical evaluation, anthropometric data were as follows: females, average height 150.6 cm (range 136–158 cm) and average weight 50.4 kg (range 33.5–78 kg); in males the average height was 157.5 cm (range 147–164 cm) and the average weight was 59.4 kg (range 39.5–98.8 kg). All of these parameters were within the WBS-specific growth charts for sex and age. Fourteen patients (31.1%) were found to be underweight, 19 patients (42.2%) had a normal weight and 8, (17.7%) half male and half female, were overweight and (8%) frankly obese.

Body weight increase in the overweight group started at a mean age of 16.6 and 21 years in males and females, respectively. In the obese group, (three males and one female) weight gain began at a mean age of 14 years in the males and 24 years in the female.

Cardiovascular Evaluation

Cardiovascular abnormalities were reported in 39 subjects (86.6%). SVAS, isolated or in association with mitral valve prolapse, was the most frequent defect (30% and 33.3%, respectively). The

TABLE I. Clinical and Instrumental Examinations Performed by Patients With WBS

Clinical evaluation	Instrumental evaluation	Biochemical evaluation
Auxological examination	Measure of height, weight, BMI (kg/hr^2), nutrition education	General laboratory evaluation including blood calcium and renal function parameters
Endocrinological	Thyroid ultrasound	TSH-FT3-FT4- anti-thyroid antibodies
Cardiovascular	24-hr blood pressure monitoring ECG, echocardiography, Echo color, Doppler ultrasound of renal vessels[a]	
Gastrointestinal	Upper abdominal ultrasound, endoscopy[a]	Screening for celic disease (anti-endomisium antibodies, anti-trasglutaminase antibodies)
Ophthalmologic	Fundus oculi, refractive errors research	
Audiologic	Audiograms	
Nephrological	Lower abdominal ultrasound	Urinalysis, creatinine serum level dosage/spot urine calcium to creatinine ratio
Gynecologic	Pelvic ultrasound, mammary ultrasound (over 30 years)	
Orthopedic	Radiographs[a]	
Odontostomatologic	Panoramic radiographs[a]	

[a]As needed.

TABLE II. The Age at Diagnosis and Need for Cardiac Intervention in Different Heart Defects

	Infants (<12 months)		Pediatric/adolescent (1–17 years)		Adults (>17 years)		Total	
Heart defect	N	Intervention	N	Intervention	N	Intervention	N	%
SVAS	3	0	9	5	0	0	12	30
SVAS + PAS	2	0	0	2	0	0	2	5.1
PAS	2	0	0	0	1	0	3	7.6
SVAS + CoA	1	0	0	1	0	0	1	2.5
SVAS + PAS + CoA + CMP	0	0	0	0	0	0	0	0
SVAS + DIV + DIA + PAS	1	1	0	0	0	0	1	2.5
Aortic valve defect	0	0	1	0	0	0	1	2.5
Mitral valve defect	1	0	4	0	1	0	6	15.3
CMP	0	0	0	0	0	0	0	
Tetralogy of Fallot	0	0	0	0	0	0	0	0
SVAS + mitral valve defect	1	0	11	0	1	1	13	33.3
SVAS + PAS + mitral valve defect	0	0	0	0	0	0	0	0
Total	11	1	25	8	3	1	39	

SVAS, supravalvular aortic stenosis; PAS, pulmonary arterial stenosis; CoA, aortic coartation; TOF, tetralogy of Fallot.

patients were divided into three groups, based on the age at the diagnosis of cardiovascular defect and the time of surgical intervention (Table II).

First diagnosis of a cardiac anomaly after 18 years of age was made in 3/39 patients (7%). In two of them the lack of prior cardiac evaluation made it impossible to assess the true age of onset of the anomalies. In one case onset of the cardiac defect (mitral valve prolapse with valve incompetence) was at 24 years. Only one adult female underwent surgical intervention to correct SVAS which was diagnosed at the age of 4.

After 24-hr blood pressure monitoring 21 subjects (46%, 13 males and 8 females), were found to be hypertensive. Mean age of onset of hypertension was 18.5 years (range 14–29). Eleven of 21 (52%) developed hypertension in adult life; 9 of them required pharmacological treatment, most commonly with beta-blockers or calcium channel blockers.

All subjects received a Doppler ultrasound evaluation of renal arteries. No sign of renal stenosis became evident in WBS adults.

Endocrine Evaluation

Thyroid function tests and thyroid ultrasonography were performed in all subjects. Average TSH level was 2.63 (range 0.98–6.78) (normal range 0.28–4.3 IU/ml), average fT3 3.6 pg/ml (range 2.2–5.6) (normal ange 0.28–4.3 pg/ml), average fT4 12.45 pg/ml (range 1.6–17.4) (normal range 8–16 pg/ml). Subclinical hypothyroidism was reported in 8/45 (17.7%) patients, without detection of thyroid antibodies. Average age at onset of subclinical hypothyroidism was 13.8 years of age (range 6–31). In two of these eight patients (25%) diagnosis was made in adult life. Neither of them needed treatment.

In 27/45 patients (60%) thyroid hypoplasia had been detected by ultrasound examination during infancy. None became worse during adulthood.

Gastrointestinal Evaluation

Twelve of 45 patients (26.6%) reported constipation present since infancy. Other gastrointestinal problems were gastroesophageal reflux in 1/45 patients (2%) which was diagnosed in adult life and treated with anti-secretory therapy and diverticolosis affecting 3/45 (7%) diagnosed because of abdominal pains and diarrhea. One of these cases, a male, was diagnosed at age 23.

Three patients (6.6%) had already been diagnosed with celiac disease, confirmed by small bowel biopsy. All others underwent serological testing for this condition (dosage of anti-endomisium and anti-transglutaminase antibodies) and no new cases of celiac disease were identified. Upper and lower abdominal ultrasound examination was carried out in all patients. Liver steatosis was observed in two subjects, but liver function tests were normal.

Orthopedic Evaluation

On physical examination, orthopedic abnormalities were present in 36/45 subjects (80%). Twenty-three presented with scoliosis, eight with lordosis, and six had isolated feet problems. Adult onset of orthopedic complications was reported in 7/36 subjects (19%). None of the orthopedic problems were severe enough to require treatment with either orthopedics devices or surgical correction. Therefore, orthopedic problems do not appear to cause severe impairment in personal level of autonomy.

Ophthalmological Evaluation

Ophthalmologic abnormalities were recorded in 29/45 subjects (64.4%), and consisted of myopia (n = 12), hyperopia (n = 8), and astigmatism (n = 9). A first diagnosis of refractory errors in adulthood was reported in 8 of these 29 patients (27%) while 4 patients needed corrective lenses.

Tortuosity of retinal vessels was reported in four subjects and was first diagnosed at mean age of 26 years (range 21–30 years). Three of them had a positive history of hypertension, first detected at the ages of 18, 29, and 35 years, respectively.

Audiologic Evaluation

Audiologic problems were recorded in 13/45 subjects (28.8%). Five (38.4%) had been diagnosed with hyperacusia, in infancy and the condition was still present at the last audiologic examination.

In 8 of these 13 subjects (61.6%) recorded audiograms showed hypoacusia including conductive hypoacusia (n = 1), mixed hypoacusia (n = 2), and sensorineural hypoacusia (n = 5). In all these hypoacusia was mild, bilateral and started in adulthood (average age of 25.5 years). No one needed hearing aids.

Dental Evaluation

Orthodontic examination showed poor oral hygiene in 14/45 subjects (31.1%), resulting in halitosis and dental caries. Orthodontic problems such as malocclusion and dental malposition had been reported in nine patients during infancy.

Nephrologic Problems

Renal function was assessed in all participants. The average creatinine level was of 0.83 mg/dl (range 0.51–1.12) (normal 0.50–1.00 - 00 mg/dl). Creatine clearance was calculated and was normal in all patients.

The mean serum calcium concentration was 9.5 mg/dl (range 5.1–10.98) (normal 8.4–10.2 mg/dl); while the mean phosphorus level was 3.66 mg/dl (range 2.2–5.9) (normal 2.7–4.5 mg/dl). Urinary calcium/creatine ratio was over 0.22 in only one subject previously measured during adolescence.

Hypercalcemia was not found in any of the adult patients. No one presented with hematuria or proteinuria.

An ultrasound examination confirmed structural anomalies already detected in infantile period in 11/45 subjects (24%). In a single female bladder diverticuli with recurrent urinary tract infection was demonstrated at 27 years of age. No patient had nephrocalcinosis.

Gynecologic Evaluation

Five of 22 adult WBS females underwent a gynecological examination. Mean age at clinical examination was 29 years (range 28–32). Mean age at menarche was 11 years (range 9–12). Menstruation was regular in 4/5 females; in one polymenorrhea was reported. Mammary ultrasound was performed in 6/22 females. Breast cysts were present in 3/6. Imaging of fibroadenomas were reported in 3/6.

Neuropsychological and Social Data

According to ICD-10 classification, IQ testing showed borderline intelligence quotient in 5/28 patients (18%), mild mental retardation in 11/28 (39%), and moderate mental retardation in 12/28 (43%) where a formal IQ test was performed.

Twenty-one of 38 subjects (55%) of the cohort were still attending school. All of them were assisted by a personal tutor or are attending classes for people with special educational needs, but 14 of them (67%) were going to vocational schools.

Twenty-seven of 38 (71%) were involved in working activities mostly connected with their educational program; according to this only 7 of them (26%) are paid for their work. Average wage was 300 euros per month. All interviewed subjects live with their families. Five of 38 (13%) were in pharmacological therapy for mood disorders.

DISCUSSION

The aim of this study was to contribute to the understanding of the progression of medical problems in adults with WBS. During the past decades only a few studies in adults have been reported in literature [Morris and Carey, 1990; Cherniske et al., 2004]. Only very recently the diagnosis and management of this condition in patients over 30 years of age has even been discussed [Pober and Morris, 2007].

In our cohort of 45 adult patients, ongoing medical problems commonly involved cardiovascular, gastrointestinal, musculoskeletal, and visual systems. Eighty-six percent of WBS patients enrolled in this study had at least one cardiovascular abnormality. SVAS was the most common (29/39) followed by peripheral pulmonary artery stenosis (5/39), as has been reported in previous studies [Eronen et al., 2002]. These heart defects were all recognized and treated when the patients were infants. Therefore, with respect to cardiac problems, adults require only a periodical monitoring and antibiotic prophylaxis when indicated.

Hypertension was reported in 46% (21/45) of our series, a frequency that is consistent with previously published data [Broder et al., 1999; Cherniske et al., 2004]. In half of them the diagnosis was made after 18 years of age by means of a 24-hr monitoring of arterial blood pressure. These data suggest that regular monitoring of blood pressure is highly recommended in adult WBS patients. Twenty-four-hour blood pressure monitoring should be the method of choice, being the most sensitive method to detect even initial signs of hypertension, such as the lack of th physiological nocturnal blood pressure decrease. None of the patients with adult onset hypertension showed a significant renal artery stenosis. Thus, this particular complication seems confined to cases of early onset of hypertension.

Orthopedic deformities such as scoliosis and lordosis were extremely common in our patients (82%). Postural abnormalities have been described previously [Morris and Carey, 1990; Lopez-Rangel et al., 1992]. A recently published list of recommendations for medical monitoring of adults with WBS [Pober and Morris, 2007] pointed out that these problems typically worsen without physical therapy, especially in adults with fixed contractures and reduced strength around the shoulder girdle. Regular stretching exercises extending the range of motion should therefore be part of the daily regimen of an adult with WBS.

Chronic abdominal pain is common in adults with WBS and half of the reported adults with WBS have chronic constipation [Pober and Morris, 2007]. Thirty-six percent of our patients reported gastrointestinal problems with constipation being the most

common, always noted in infancy. No adult onset of constipation was noted. Diverticular disease was noted in only one patient (2%) in young adult age, a rate far lower than that reported by Cherniske et al. [2007] who found a frequency of diverticular disease in WBS patients younger than 40 years of age that was three to four times higher than that of general population.

Serological screening for celiac disease was performed because Giannotti et al. [2001] showed that 10% of the children with WBS have a positive antibody evidence for celiac disease. None of our patients were found to be serologically positive. Published data about the incidence and age of onset of celiac disease in WBS patients are neither numerous nor detailed. Therefore, it is not possible to define a specific age at which this screening could be stopped even if it seems that the risk in adulthood is low.

Formal ophthalmologic examination was performed in all of our patients. Visual system problems were reported in 62% of them; this result is similar to findings of other studies with comparable data collection methods [Lopez-Rangel et al., 1992; Cherniske et al., 2007]. Strabismus (present in half of our patients) and refractive problems were the most common defects observed. It is remarkable that in one-third of our patients the diagnosis of ophthalmologic problems was made after 18 years of age, stressing the importance of carrying out eye examinations in adult WBS patients.

Hyperacusia and phonophobia are known findings in children affected by WBS. In older patients, mild to moderate high-frequency sensorineural hearing loss is described [Marler et al., 2005; Gothelf et al., 2006]. In our cohort 61% presented with hypoacusia with onset after 18 years of life, again demonstrating the importance of regular evaluations at this age.

Our experience with adults with WBS showed that poor dental hygiene was a frequent problem to be solved. The poor visual skills and the intrinsic deficiencies of tooth integrity have led to caries and periodontal disease [Pober and Morris, 2007].

There are published reports concerning renal dysfunction in the WBS literature [Davies et al., 1997]. None of the members of our cohort had evidence of renal disease such as nephrocalcinosis, renal litiasis, or reduced renal function. Eleven of 45 (24%) experienced urinary tract structural abnormalities at abdominal ultrasound examination. This percentage is consistent with previously reported studies [Pankau et al., 1996; Sforzini et al., 2002].

The most commonly reported endocrine abnormality in WBS is infantile hypercalcemia [Morris et al., 1988; Jones, 1990]. The incidence of hypercalcemia was estimated to be about 15%. In our cohort we had one case of infantile hypercalcemia, but none of our patients showed an increased concentration of calcium in adult life.

There have been recent reports of thyroid abnormalities primarily on children with WBS. In the current series of WBS adults thyroid function was assessed for 28/45 subjects. HyperTSH was reported in eight subjects, but in only two of them (25%) the diagnosis had been made in adulthood. As reported previously hypoplasia of the thyroid gland was present in the majority of our cohort, but no worsening was observed during follow-up in adult life [Selicorni et al., 2006]. These results suggest that after adolescence thyroid ultrasound examination in the absence of clinical symptoms is not warranted.

Regarding gynecological aspects, few WBS adult females underwent a gynecological examination. None of five female showed specific gynecological problems (precocious puberty or menopause, PCO). None had been pregnant. Unlike the data published by Cherniske et al. [2004] none of them had undergone hysterectomy or received estrogen replacement therapy, but these data need to be corroborated by additional observations.

Finally our data about IQ testing overlap with those already described by other authors in patients affected by Williams syndrome.

What emerges from our survey is that young adults with WBS in Italy are well cared for as long as they attend school, but the

TABLE III. Possible Indications for Medical Monitoring of Adults Followed From Childhood With WBS

Clinical evaluation	Instrumental evaluation	Biochemical evaluation
Auxological examination	Measure of height, weight, BMI (kg/hr^2), nutrition education	General laboratory evaluation
Endocrinological	Thyroid ultrasound[a]	TSH-FT3-FT4- anti-thyroid antibodies[a], OGTT
Cardiovascular	24-hr blood pressure monitoring ECG, echocardiography, Echo color, Doppler ultrasound of renal vessels[a]	
Gastrointestinal	Upper abdominal ultrasound, endoscopy[a]	Screening for coelic disease (anti-endomisium antibodies, anti-trasglutaminase antibodies)[a]
Ophthalmologic	Fundus oculi, refractive errors research	
Audiologic	Audiograms	
Nephrological	Lower abdominal ultrasound	Urinalysis, creatinine serum level dosage/spot urine calcium to creatinine ratio
Gynecologic	Pelvic ultrasound, mammary ultrasound (over 30 years)	
Orthopedic	Radiographs[a]	
Orthodontics/dental	Panoramic radiographs[a]	

[a]As needed.

TABLE IV. Possible Indications for Medical Monitoring of Recently Diagnosed Adults With WBS

Clinical evaluation	Instrumental evaluation	Biochemical evaluation
Auxological examination	Measure of height, weight, BMI (kg/hr^2), nutrition education	General laboratory evaluation including blood calcium and renal function parameters
Endocrinological	Thyroid ultrasound	TSH-FT3-FT4- anti-thyroid antibodies
Cardiovascular	24-hr blood pressure monitoring ECG, echocardiography, Echo color, Doppler ultrasound of renal vessels[a]	
Gastrointestinal	Upper abdominal ultrasound, endoscopy[a]	Screening for celic disease (anti-endomisium antibodies, anti-trasglutaminase antibodies)
Ophthalmologic	Fundus oculi, refractive errors research	
Audiologic	Audiograms	
Nephrological	Lower abdominal ultrasound	Urinalysis, creatinine serum level dosage/spot urine calcium to creatinine ratio
Gynecologic	Pelvic ultrasound, mammary ultrasound (over 30 years)	
Orthopedic	Radiographs[a]	
Orthodontic/dental	Panoramic radiographs[a]	

[a]As needed.

transition to work is not systemized. A better characterization of the social, working, and living opportunities of these patients should be systematically obtained.

CONCLUSION

It is possible to conclude, from our clinical data, that elastin gene haploinsufficiency might be responsible for an increased incidence of arterial hypertension, intestinal and bladder diverticolosis, functional spine anomalies, refractive visual problems, sensorineural hypoacusia. It is also interesting that an unusual high percentage of our patients are overweight. These results are quite similar to those published in adult patients affected by completely different MCA/MR syndromes. It could be interesting to compare these data to other genetic diseases in order to discriminate if these trends are disease specific or common to MR syndromic adult patients.

All these observations support the importance of a long-term specific and multidisciplinary follow-up in adult patients with WBS. The protocol should be tailored to each individual patient's clinical situation. On the basis of our experience we have summarized our suggested protocol of evaluation and follow-up in patients with WBS followed since infancy (Table III) and in recently diagnosed adults (Table IV).

ACKNOWLEDGMENTS

We thank the Mariani Foundation for supporting the clinical activities of the Ambulatorio di Genetica Clinica and the patients and their parents of Associazione Italiana Sindrome di Williams for their constant and global collaboration. We would also like to thank Dr. C. Gagliardi, Dr. R. Grasso, Dr. R. Borgatti, IRCCS Istituto E. Medea, Bosisio Parini (LC), Dr. E. Vismara, Unità di oculistica, Dr. U. Valadè, Unità di Chirurgia, Dr. M. Orsi and Dr. L. Fugazzola, Unità di Endocrinologia, Dr. S. Di Gironimo, Unità di Radiologia, Dr. U. Ambrosetti, Unità di Audiologia, prof. Miragoli, Unità di Ostetricia e ginecologia, Dr. P. Salice and Dr. A. Galli, UO Cardiologia, Dr. E. Cristini, Unità di traumatologia, Fondazione IRCCS Ca Granda, Ospedale Maggiore Policlinico, Milan and Dr. A. Memeo, Istituto Ortopedico G.Pini, Milan, for their multidisciplinary contribution to evaluate the patients.

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