

Research Review

Rubinstein-Taybi Syndrome Medical Guidelines

Susan Wiley,^{1*} Susan Swayne,² Jack H. Rubinstein,³ Nancy E. Lanphear,³ and Cathy A. Stevens⁴

¹Children's Hospital Medical Center, Division of Developmental Disabilities, 3333 Burnet Ave., Cincinnati, Ohio

²81st MDOS/SGOC, 301 Fisher St., Keesler Air Force Base, Mississippi

³University of Cincinnati College of Medicine, Department of Pediatrics, Children's Hospital Medical Center, Division of Developmental Disabilities, 3333 Burnet Ave., Cincinnati, Ohio

⁴Department of Pediatrics, University of Tennessee College of Medicine-Chattanooga Unit, T.C. Thompson Children's Hospital, 910 Blackford Street, Chattanooga, Tennessee

Children and adults with Rubinstein-Taybi Syndrome have specific medical conditions that occur with greater frequency than the general population. Based on the available information from the literature and clinical experience, recommendations for specific surveillance and interventions are made to guide those clinicians caring for individuals with Rubinstein-Taybi Syndrome. This is a first attempt at medical guidelines for individuals with RTS in the United States. Ongoing research is needed in many areas to guide decisions in medical care and allow for refinement of these medical guidelines.

© 2003 Wiley-Liss, Inc.

KEY WORDS: Rubinstein-Taybi syndrome; broad thumb-hallux syndrome; medical guidelines

INTRODUCTION

Children with Rubinstein-Taybi Syndrome (RTS or RSTS) should follow the standard health recommendations and developmentally appropriate anticipatory guidance that apply to all children. Children with RTS have additional health concerns associated with the syndrome that require monitoring and evaluation. These guidelines are based on the available evidence

Grant sponsor: Maternal and Child Health Bureau, Health Resources and Service Administration, DHHS; Grant number: 2 T73 MC 00032-11; Grant sponsor: Administration on Developmental Disabilities, Administration for Children and Families, DHHS; Grant number: 90DD0426/05.

*Correspondence to: Susan Wiley, Children's Hospital Medical Center, Division of Developmental Disabilities, 3333 Burnet Ave., Cincinnati, OH 45229. E-mail: wiles0@chmcc.org

Received 24 January 2002; Accepted 19 August 2002
DOI 10.1002/ajmg.a.10009

from the world literature of children and adults with RTS as well as those individuals seen personally by or have had personal communication with Dr. Rubinstein with documented Rubinstein-Taybi Syndrome. These guidelines are also a collaborative effort with specialist clinicians who care for individuals with RTS. In some cases, there are insufficient data to support specific recommendations for the population of individuals with RTS. Data on adults with RTS are limited and are currently being gathered. Each person should have an individualized approach to health care. Growth grids for RTS (Figs. 1–4) and health maintenance checklists are included (Figs. 5 and 6).

DIAGNOSTIC FEATURES

Individuals with RTS have distinctive features which can include: palpebral fissures slanting down towards the ears, apparent hypertelorism, long eyelashes, high-arched eyebrows, prominent nose with columella below the alae nasi, malpositioned ears with dysplastic helices, grimacing smile, high arched palate, hypoplastic maxilla, broad thumbs and toes (broad, short terminal phalanges of the thumbs and halluces with or without angulation deformity), persistent digital fetal pads, and postnatal growth retardation and head circumference below the 50th percentile. X-rays of the hands and feet with the thumbs pressed flat can be helpful to identify the radiologic findings which can include: delta-shaped proximal phalanges of the thumbs, small hole or distal notch in the distal phalanx which is short and broad, angulation of the distal phalanges, duplication of the proximal and/or distal phalanges of the large toes, and angulation deformity of the hallux. There also are a number of medical issues that occur commonly in individuals with RTS. These can include significant gastroesophageal reflux, feeding difficulties, constipation, hypotonia, congenital heart disease, renal anomalies, problems with anesthesia, ophthalmologic problems, orthopedic problems, developmental delay, and mental retardation. There is wide variability of the phenotypic appearance in individuals

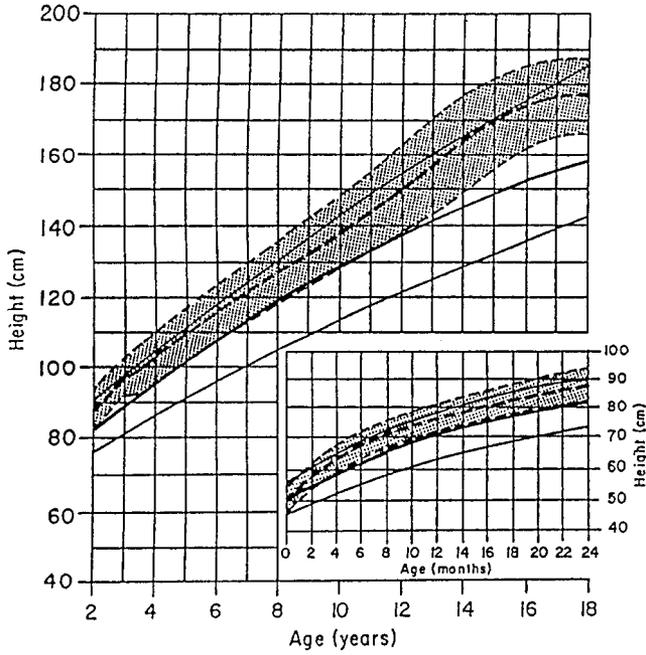


Fig. 1. Height curve of males with Rubinstein-Taybi syndrome (solid lines) compared with normal males (dashed lines). From Stevens et al. [1990b].

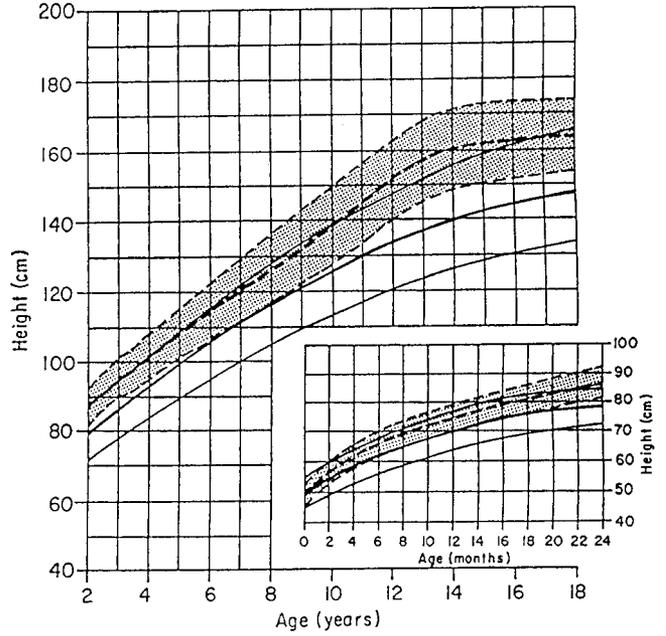


Fig. 3. Height curve of females with Rubinstein-Taybi syndrome (solid lines) compared with normal females (dashed lines). From Stevens et al. [1990b].

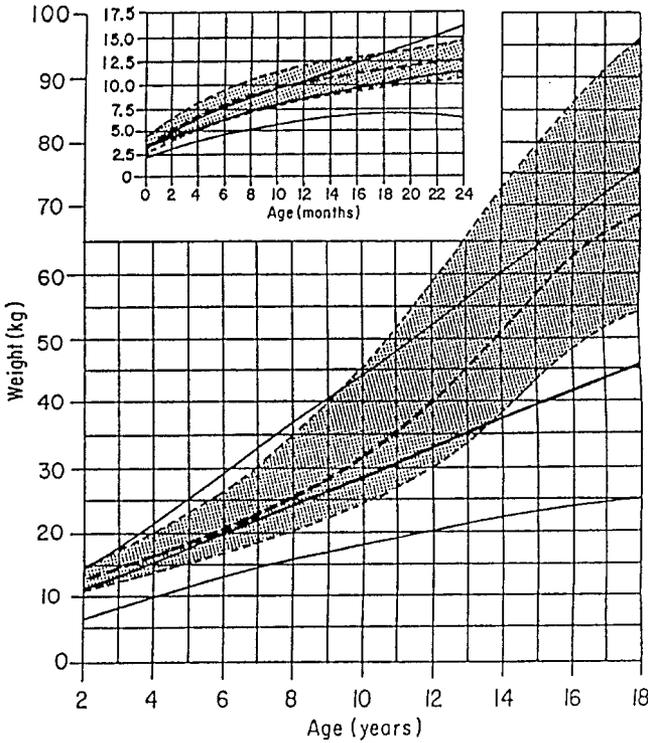


Fig. 2. Weight curve of males with Rubinstein-Taybi syndrome (solid lines) compared with normal males (dashed lines). From Stevens et al. [1990b].

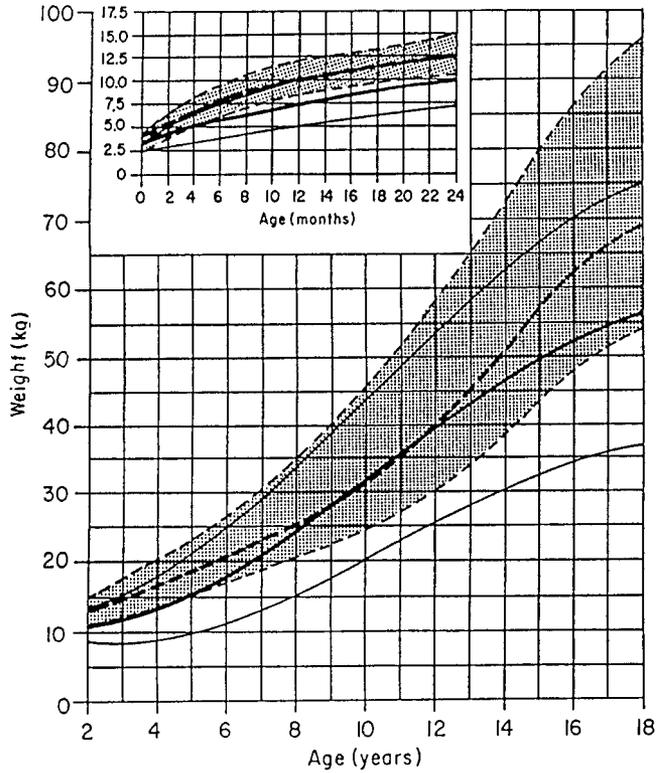


Fig. 4. Weight curve of females with Rubinstein-Taybi syndrome (solid lines) compared with normal females (dashed lines). From Stevens et al. [1990b].

**Rubinstein-Taybi Syndrome Health Care Guidelines
Birth to Age 12 Years**

Name: _____ Date of Birth: _____

Medical Issues	At Birth or at Diagnosis	Age, in years														
		6-mo	1	1-1/2	2	2-1/2	3	4	5	6	7	8	9	10	11	12
Usual Practice & Care																
Cardiology ¹	Cardiologist, Echo, EKG															
Renal	US, +/-VCUG															
Audiologic Evaluation	ABR or OAE															
Ophthalmologic ² Evaluation																
Physical Exam w/focus on Neurologic and Orthopedic Examination																
Nutrition																
Dental Exam ³																
Family Support Resources																
Developmental & Educational Services	Early Intervention															
Genetic Counseling																

Instructions: Perform indicated exam/screening and record date in blank spaces. The grey or shaded boxes mean no action is to be taken for those ages.

¹Ongoing appointments with cardiology as based on the diagnosis.

²More frequent appointments depending on diagnosis and need for intervention.

³Begin dental exams at 1 years of age and continue every 6 months thereafter.

Fig. 5. Health maintenance checklist I.

with RTS. Pictures can be helpful in identifying the changes that can occur to the facial features of individuals with RTS over time [Allanson and Hennekam, 1997].

BASELINE STUDIES

- Regardless of the age of diagnosis:
- Pediatric geneticist knowledgeable in dysmorphology, and developmental pediatrician evaluation.
 - Electrocardiogram, echocardiogram and examination by a pediatric cardiologist.
 - Full ophthalmologic examination by a pediatric ophthalmologist.
 - Renal ultrasound and consideration of a voiding cystourethrogram (VCUG).
 - Hearing evaluation.

BY SYSTEM

Anesthesia

Ideally children with RTS undergoing general anesthesia should be under the care of a pediatric anesthe-

siologist or adult anesthesiologist comfortable with complex pediatric airway problems. Children with RTS require appropriate monitoring due to airway anomalies [Critchley et al., 1995], skeletal anomalies, increased risk of aspiration, and cardiac anomalies. Children with RTS are more challenging to intubate due to their relatively anterior larynx [Allanson, 1990] and easy collapsibility of the laryngeal wall. Intubation with anesthesia is important due to the high risk of aspiration during induction and emergence. There have also been reports of cardiac arrhythmia with the use of cardioactive drugs (atropine, neostigmine, and succinylcholine) [Stirt, 1981; Stirt, 1982].

Cardiac

All children should receive an evaluation by a pediatric cardiologist, baseline electrocardiogram, and echocardiogram as 24–38% of children with RTS have cardiac abnormalities [Hennekam et al., 1990b; Rubinstein, 1990; Stevens and Bhakta, 1995]. (These include ASD, VSD, PDA, coarctation of the aorta, pulmonic stenosis, bicuspid aortic valve, pseudotruncus, aortic

Rubinstein-Taybi Syndrome Health Care Guidelines 13 Years to Adulthood

Name : _____ Date of Birth: _____

Medical Issues	Age, in years							
	13	14	15	16	17	18	19	20
Usual Practice & Care								
Audiologic Evaluation								
Ophthalmologic Evaluation								
Physical Examination with focus on orthopedic and neurologic exam								
Nutrition								
Dental Exam SBE prophylaxis Y ___ N ___								
Family Support Resources								
Developmental & Educational Services								
Pelvic Exam								
Assess Contraceptive Need								

Instructions: Perform indicated exam/screening and record date in blank spaces. The grey or shaded boxes mean no action is to be taken for those ages.

¹Begin dental exams at 1 years of age and continue every 6 months thereafter.

Fig. 6. Health maintenance checklist II.

stenosis, dextrocardia, vascular rings, and conduction problems.) If an abnormality is found, on-going care and monitoring by a cardiologist is warranted.

SBE prophylaxis should be instituted for individuals at risk [Dajani et al., 1997].

All individuals with RTS should have yearly blood pressure monitoring beginning at the age of 3 years. Obstructive sleep apnea may contribute to hypertension in individuals with RTS [Surdulescu et al., abstract]. Polysomnography in individuals with RTS and hypertension should be considered (for other indications for polysomnography, see section on respiratory).

Dental

All children with RTS should have dental exams by a pediatric dentist every 6 months beginning at 1 year of age. Adults with RTS should be seen by a dentist comfortable with adults with disabilities. Individuals with RTS may require more frequent dental visits depending on findings. Common findings in individuals with RTS include talon cusps of secondary dentition (which can contribute to grinding down of the tooth to expose the

pulp), crowding and malpositioned teeth, anterior and posterior crossbites secondary to a narrow palate or jaw size discrepancy, natal teeth, gingivitis, hypo- and hyper-dontia [Kinirons, 1983; Baker, 1987; Rubinstein, 1990; Hennekam et al., 1990a; Taylor and Callen, 1999]. Dental abnormalities occur in 67% of individuals with RTS [Rubinstein, 1990]. Parents report problems in daily tooth care in 43% mainly due to inadequate brushing because of irregularly formed and placed teeth [Hennekam et al., 1990a]. There is an increased rate of caries in individuals with RTS (15–36%).

If dental work on a child with RTS needs to be done with heavy sedation or anesthesia, a pediatric anesthesiologist should be present (see recommendations regarding anesthesia).

All children with RTS should have normal anticipatory guidance regarding milk bottle caries, brushing, sealants, and fluoridation as children with RTS have normal timing of eruption of deciduous and permanent teeth [Hennekam and Van Doorne, 1990; Hennekam et al., 1990a].

Orthodontia may be a consideration for individuals with RTS as the overcrowding can contribute to diffi-

culty in regular oral care [Hennekam et al., 1990a]. Orthodontia may be unattainable or the goals of orthodontia may vary due to the severity of the presenting malocclusion and/or lack of cooperation in a typical dental setting. Compliance with multiple adjustments may vary from individual to individual [Taylor et al., 1999].

Dermatologic

Surgeons should be aware that adolescents and adults with RTS have a higher likelihood to form keloids and hypertrophic scars [Siraganian et al., 1989; Hennekam et al., 1990a; Stevens et al., 1990a]. Prevention strategies are not known. Keloids can occur spontaneously, after skin trauma, and after surgery. Referral to a dermatologist for treatment of symptomatic keloids may be helpful. Prevention strategies such as silicone gel sheathing may be helpful post-operatively. Radiation therapy is not recommended for use in children.

Management of ingrown toenails and early treatment of paronychia is warranted (fingernail paronychia in 9%, toenail paronychia in 44%) [Hennekam et al., 1990a].

Individuals with pilomatrixomas should be referred to a dermatologist for excision and pathologic evaluation of the lesion [Miller and Rubinstein, 1995; Masuno, 1998].

Ears/Hearing

An ABR should be obtained in the neonatal period (by 3 months of age).

Yearly hearing tests by audiologists are indicated. Hearing tests should occur more frequently if concerns arise (i.e., multiple OM (otitis media), parental concern, and language concern) as children with RTS can have mild degrees of hearing loss (24%) [Stevens et al., 1990a].

Children with RTS should be referred to a pediatric otolaryngologist for recurrent or refractory OM as middle ear disease is more common (50%) [Stevens et al., 1990a] and more severe (risk of perforation) in children with RTS as compared to the general population. Referral is also indicated for management of hearing loss.

Endocrine

Endocrinological work-up should be based on presenting symptoms. There have been case reports of problems with glucose metabolism (hyper- and hypo-glycemia diabetes) [Rubinstein, 1990; Wyatt, 1990]. Neonates who are symptomatic should have serum glucose drawn. Thyroid [Olsen and Koenig, 1997] and indirect measures of growth hormone have usually been normal in individuals with RTS in the available literature.

Data on the need, effectiveness, or safety of growth hormone in children with RTS are not yet available.

Gastrointestinal

Aggressive medical assessment and treatment of gastroesophageal reflux (GER) is warranted in children with RTS as nutritional/feeding problems and GER associated respiratory problems are common [Grunrow,

1982; Hennekam et al., 1990a; Rubinstein, 1990; Roberts, 1996]. Referral to a pediatric gastroenterologist is recommended for refractory cases. Some children have required surgical intervention.

Constipation (40–74%) should be aggressively medically managed with dietary and medical manipulation [Hennekam et al., 1990a; Rubinstein, 1990; Stevens et al., 1990a]. There is not an increased incidence of anatomic abnormalities or Hirschsprung disease (1 case report) causing constipation reported in children with RTS. Therefore, the history and physical exam with focus on the abdominal exam, placement of anus, rectal exam, and neurologic exam as is typical for any child is sufficient. Subsequent work-up should be based on clinical suspicion, history, and physical findings.

There have been adolescents with RTS who develop dysphagia, some with esophageal pathology (strictures, post-cricoid webs, [Scott et al., 2000] vascular rings). Evaluation for anatomic issues should be considered.

Genetics

All individuals with presumed Rubinstein-Taybi Syndrome should be evaluated by a pediatric geneticist knowledgeable in dysmorphology to confirm the diagnosis.

RTS has been linked to chromosome 16p13.3. Fluorescent in Situ Hybridization (FISH) probes specific for chromosome region 16p13.3 (including 5 cosmid probes containing almost the entire gene) can identify microdeletions in approximately 10% of individuals with RTS. The probes contain regions of the cyclic AMP-responsive binding gene (*CBP* gene). A deletion positive study can be confirmatory, but a negative study does not rule out the diagnosis of RTS. The diagnosis of RTS continues to be made primarily by clinical examination. There do not appear to be phenotypic differences between individuals with and without confirmed deletions [Wallerstein et al., 1997; Blough et al., 2000; Petrij et al., 2000].

The prevalence of RTS has been estimated to be 1 in 100,000 to 125,000 live births in the Netherlands. The recurrence risk for siblings is thought to be 0.1% based on empiric data. The recurrence risk for offspring of affected individuals could be as high as 50%, particularly in individuals with deletions [Hennekam et al., 1990a].

Research on gene studies is ongoing. Continued genetic research of individuals with RTS who do not exhibit the 16p13.3 microdeletion is needed.

Genitourinary

All children with RTS should receive a baseline renal ultrasound as 52% have kidney anomalies or disease. (i.e.: hydronephrosis, duplications, vesicoureteral reflux, urinary tract infections, stones, and nephrotic syndrome) [Tanphaichitr et al., 1979; Rubinstein, 1990; Stevens et al., 1990a; Hennekam et al., 1990]. If abnormalities are found, a fluoroscopic voiding cystourethrogram (VCUG) is warranted.

A significant number of boys with RTS have incomplete or delayed descent of testes (78–100%) [Hennekam et al., 1990; Rubinstein, 1990; Stevens et al., 1990a].

Evaluation by a pediatric urologist is warranted by 6–12 months of age if the testes have not descended as is recommended for the general population [Callahan, 2000]. Many boys with RTS require orchiopexy.

If an individual with RTS has evidence of neurogenic bladder, or a change in bowel or bladder function, an evaluation for tethered cord by MRI with cine is indicated (based on case reports of tethering) [Rosenbaum et al., 1990].

Constipation (40–74%) [Hennekam et al., 1990; Stevens et al., 1990a; Rubinstein, 1990] should be aggressively treated as this can contribute to difficulties with urinary tract infections and vesicoureteral reflux (see further recommendations in section on Gastroenterology).

Growth and Nutrition

Feeding difficulties (71–80%) are common in infants with RTS [Hennekam et al., 1990; Stevens et al., 1990a; Rubinstein, 1990] and should be closely monitored with interventions instituted for oral-motor coordination difficulties (poor nipple grasp 35%, swallowing difficulties 34%), or failure to thrive (34%) [Holland, 1996; Moe et al., 1998]. Hypotonia and subsequent effects on feeding can also lead to inadequate intake of calories. Some children with RTS have oral-motor hypersensitivity and difficulty with advancing textures of foods. Consultation with pediatric registered dietitians, feeding specialists, occupational therapists, speech pathologists, and/or lactation consultants should be used if concerns arise. Breastfeeding and proper positioning for feeding is encouraged [Moe et al., 1998] (see section on Gastroenterology regarding GERD, anatomic considerations).

Neonates and children with RTS should have weight, height, head circumference, and weight for height, plotted on RTS growth grids [Stevens et al., 1990a] (Figs. 1–4) as well as on NCHS growth grids at well child visits. Using an RTS growth grid may provide evidence against failure to thrive and avoid overfeeding. Body mass index (BMI) is also helpful in monitoring growth, particularly in older children who may become overweight [Stevens et al., 1990a]. Short stature (78%) [Hennekam et al., 1990; Stevens et al., 1990a; Rubinstein, 1990], microcephaly (35–94%) [Allanson, 1993; Hennekam et al., 1990; Stevens et al., 1990a; Rubinstein, 1990] and delayed bone age (74%) are common. An increase in head circumference across percentiles should prompt a thorough neurologic exam and consideration of imaging studies to look for CNS tumors or hydrocephalus from other causes [Siraganian et al., 1989].

Growth and dietary monitoring should be ongoing with referral to a registered dietician if concerns arise. Overfeeding in the neonatal period, infancy, childhood, and adulthood should be discouraged. Prevention strategies are important to prevent increased weight for height or increased BMI (obesity) [Stevens et al., 1990a].

There are no data to support specialized diets. Specific dietary interventions should be evaluated by a nutritionist or pediatrician for safety and effectiveness.

Gynecological/Sexual Development

In adolescents reported with RTS, sexual development usually appeared normal [Hennekam et al., 1990; Stevens et al., 1990a]. The average age of onset of puberty was 12.2 years with a range of 11–13 years (case series of 14 adolescents, 4 females, and 10 males) [Stevens et al., 1990a]. The average age of menarche was 13.6 years with a range of 11–19 years (case series of 18 adolescent girls) [Hennekam et al., 1990]. Unusually heavy periods may warrant further evaluation by a gynecologist knowledgeable in caring for adolescents with developmental disabilities (case report of a bifid uterus associated with menometrorrhagia and a case report of a paratubal cystadenoma) [Lahlou and Carrier, 1971].

Developmentally appropriate sexual education strategies should be encouraged throughout the lifespan.

Hematology/Oncology/Immunology

Individuals with RTS appear to have an increased risk of benign and malignant tumors as well as leukemia and lymphoma [Siraganian et al., 1989; Miller and Rubinstein, 1995]. A low threshold for evaluating symptoms with appropriate imaging and laboratory testing is warranted.

Although there are case reports of children with RTS with an element of immune deficiency [Rivas et al., 1980; Kimura et al., 1993; Villella et al., 2000] contributing to frequent significant infections, there is to date no systematic study of the function of the immune system of individuals with RTS to suggest all children should undergo an immune work-up. Significant infections (sepsis, multiple hospitalizations for infections) may warrant further investigation of immune status. Subsequent treatment should be based on the specific immune deficiency identified and paired with the risks and benefits of treatment.

In a patient series, parents have reported a 5% complication rate for immunizations which include high fever, low grade fever, irritability, and/or vomiting [Stevens et al., 1990a]. In children without RTS who have seizures, the risk of seizures after immunization with the MMR is slightly increased. The decision to give pertussis vaccine to any child with seizures should be based on the individual risks and benefits. [American Academy of Pediatrics, 2000] There are no absolute contraindications to immunizations in children with Rubinstein-Taybi Syndrome.

Neurologic

If there are concerns regarding seizures or staring spells in children with RTS, evaluation and treatment by a pediatric neurologist is warranted (27–28% with seizures, 57–66% with abnormal EEG findings) [Hennekam et al., 1990; Rubinstein, 1990].

Cognitive/developmental regression is not expected and should be urgently evaluated. If children have new onset neurologic findings, increase in head circumference across percentiles, or symptoms of increased intracranial pressure, aggressive work-up is indicated as

there is an increased risk of neural tumors [Siraganian et al., 1989; Miller and Rubinstein, 1995; Skousen et al., 1996; Burton et al., 1996]. Spinal cord malformations (spinal cord tethering, lipoma, thickened filum terminale) [Hennekam et al., 1990; Rosenbaum et al., 1990] have been reported. Imaging studies should relate to the presenting symptoms and neurologic examination findings.

Ophthalmologic

All children with RTS should have a complete ophthalmologic evaluation by a pediatric ophthalmologist shortly after the time of diagnosis or by 6 months of age if identified in the neonatal period. Referral to an ophthalmologist should occur earlier if there are concerns. Ongoing and regular ophthalmologic care is indicated at 12-months interval or more frequently as determined by findings.

Suspicion of glaucoma or corneal opacities requires urgent evaluation by a pediatric ophthalmologist. Measurement of intraocular pressure usually requires examination under anesthesia. Anesthesia may falsely lower the intraocular pressure. Therefore, measurement of intraocular pressure should be done in the early stages of anesthesia [Burke, 1998]. Any anesthesia should be performed with a pediatric anesthesiologist (see recommendations regarding anesthesia). Ocular findings in individuals with RTS that mimic glaucoma include corneal lesions, megalocornea, colobomatous or cystic optic nerve, excavation of papilla, and large cup-to-disc ratio [Brei et al., 1995]. Intraocular pressure monitoring should be obtained at the time of concern.

There is a high occurrence of a variety of ocular findings (80%) which can impact vision, particularly refractive errors and strabismus [Roy et al., 1968; Hennekam et al., 1990; Rubinstein, 1990; Stevens et al., 1990a; Burke, 1998]. These usually respond well to interventions. Ocular findings include the following: strabismus 60–71% with subsequent risk of amblyopia, refractive errors 41–56%, ptosis 29–32%, Duane retraction syndrome 8%, and coloboma 9–11% [Hennekam et al., 1990; Rubinstein, 1990; Stevens et al., 1990a; Ge et al., 1995]. There have been occurrences of ghost vessels, Peters anomaly, optic nerve hypoplasia, cataracts, and corneal opacities.

Children with RTS have a higher frequency of lacrimal duct obstructions (38–47%) [Roy et al., 1968; Stevens et al., 1990a; Brei et al., 1995; Burke, 1998]. This may require surgical intervention if it does not resolve.

Orthopedic

Children with significant angulation of their thumb should be considered for surgical repair prior to the age of 2 years as the angulation can impact functional ability [Wood and Rubinstein, 1987; Cerqueiro-Mosquera and Fleming, 2000].

Individuals with RTS may require surgical repair of their first toe for duplicated longitudinal bracketed epiphysis. This should occur between the ages of

6 months to 1 year or at any age if there is pain with footwear [Wood and Rubinstein, 1999].

Children with RTS should have their elbows examined periodically. A prominent bump laterally at the elbow along with limitation in range of motion of the elbow should alert the clinician to dislocation of the radial head. Children with RTS have an incidence of dislocation of the radial head of 2%, which is 11 times greater than the general population.

Children with RTS may require surgical repair for patellar dislocation to improve outcomes for ambulation and motor skills [Stevens, 1997; Mehlman et al., 1998].

Children with RTS should have regular joint exams and neonatal and infant hip exam with a low threshold for pediatric orthopedic referral. There are also established associations with hypotonia, lax ligaments, tight heelcords, elbow abnormalities, Legg-Perthes (3%), dislocated patella (2.5%), congenital hip dislocation (1.4%), and slipped capital femoral epiphysis (SCFE) (0.6%) [Hennekam et al., 1990; Rubinstein, 1990; Bonioli et al., 1993; Mehlman et al., 1998]. Pain or a change in gait should be evaluated urgently. In Perthes, the hip exam shows decreased abduction. In SCFE, the hip has obligate external rotation upon hip flexion. There is a loss of internal rotation and the hip tends to be externally rotated. Genu valgum should be evaluated with a supine assessment of the intermalleolar distance. If the distance is greater than 8–10 cm, referral to a pediatric orthopedic surgeon is warranted.

Children with RTS seem to have an increased risk of fractures [Hennekam et al., 1990; Rubinstein, 1990]. Evaluation of pain or change in gait should take this into consideration.

Children with RTS can have congenital or acquired scoliosis, kyphosis, and lordosis [Hennekam et al., 1990; Rubinstein, 1990; Stevens et al., 1990a]. They should have yearly screening exams for scoliosis as part of their well child-care beginning the age of 10 years in boys and girls (based on an approximation using RTS growth grids' mid-point of the final growth spurt and consideration of pubertal development).

All children with RTS should have an ultrasound of the spine in the neonatal period due to an increased risk of thickened filum terminale, tethering of the cord, and lipoma [Rosenbaum et al., 1990]. If the ultrasound is abnormal, confirmation by MRI with cine is indicated. An MRI with cine is warranted in older symptomatic children (change in bowel or bladder habits, change in gait). If a child is not identified as having RTS until after the neonatal period, imaging should be based on symptoms and physical exam findings (tuft of hair, mass, sacral dimple, hemangioma, or abnormal pigmentation over the lumbosacral region).

Respiratory

Children with RTS can have upper airway obstruction [Zucconi et al., 1993] during sleep due to hypotonia, anatomy of the oropharynx and airway (small nasal passages, retrognathia, micrognathia, hypertrophy of the tonsils and adenoids) [Allanson, 1990] and obesity. Children with craniofacial anomalies have abnormal

polysomnography results in 20–30% as compared to 1–3% in the general population. It is unclear if this can be extrapolated to children with RTS. Routine polysomnography under the care of a pediatric pulmonologist is currently under study. Children with RTS who have snoring, respiratory pauses, nighttime sweating, abnormal sleep positions (i.e., sleeping upright), and/or restless sleep should be considered for an overnight polysomnography [Zuconi et al., 1993, Surdulescu et. el. abstract]. Appropriate medical and surgical treatments should be instituted based on these results. The general population peaks for sleep apnea at the age of 3–4 years. Repeat testing should be considered between this age span or at any age if there is a concerning history of sleep apnea, change in snoring or an excess weight gain. Hypertension should also warrant consideration of polysomnography. Tonsillectomy and adenoidectomy (T&A) has been helpful in some children. This should be performed with caution due to the airway and anesthesia issues in individuals with RTS. Other interventions may be needed if T&A is not effective. Children may require follow-up polysomnography if the study was markedly abnormal prior to intervention.

Children with RTS who present with frequent upper respiratory infections, multiple episodes of pneumonia or wheezing, hoarseness, or stridor should be evaluated for GER and aspiration contributing to these symptoms [Hennekam et al., 1990; Rubinstein, 1990]. Work-up for anatomic and immune considerations should be based on clinical suspicion. Vascular rings [Sashi and Fryburg, 1995], post-cricoid web [Scott et al., 2000], submucous cleft palate, and abnormalities of the bronchial tree (personal experience, Rubinstein) have been reported.

Symptoms of asthma have been reported by parents [personal experience Rubinstein and Gordeev, 1977]. Evaluation and standard treatment for asthma is appropriate.

Developmental/Behavioral/Emotional

Referral to Early Intervention Programming is indicated due to the developmental delays [Hennekam et al., 1990] seen in children with RTS. Specific private therapies (early childhood specialist, occupational, physical, and speech therapy) should be instituted on an individual basis. Estimation of long-term functioning is not possible at a young age.

Parents should be encouraged to learn of their rights within the early intervention and educational systems as most children with RTS require some degree of individualized programming, whether in specialized or inclusive settings (range of FSIQ: 30–79) [Hennekam et al., 1990; Stevens et al., 1990a].

Speech delay occurs in 90% [Stevens et al., 1990a]. Some individuals are non-verbal and use sign language or augmentative systems as their predominant mode of communication.

Children with RTS are often described by their families as loving, friendly, and happy [Stevens et al., 1990a].

Referral to pediatric behavioral specialist, psychologist, or child psychiatrist, knowledgeable in the field of developmental disabilities for behavior management

strategies should be instituted if a child with RTS has concerning behaviors (survey of parent reported behaviors include: repetitive motions, resistance to change, distractibility, aggressive outbursts, and difficulty in sleeping) [Stevens et al., 1990a, 1999; Taff and Madad, 1998].

In adults with RTS, mood disorders, tic/OCD spectrum, self-injurious behaviors, and autistic features have been described [Levitas and Reid, 1998].

Consideration of medication for behavior refractory to behavioral interventions may be warranted. Effectiveness of medication and side effects should be cautiously monitored as neuroleptic malignant syndrome and neuroleptic-induced movement disorders were found to be common in adults with RTS [Levitas and Reid, 1998]. There is currently a study underway for medication use in children with RTS.

Referral to the local system for children and adults with disabilities may allow access to behavioral interventions. Each state has a Developmental Disabilities Planning Council which can refer to local support systems. The ARC is a resource, which may be able to identify additional local resources.

Family Support/Resources

Referral to local support groups for parents of children with special needs can be quite helpful.

Specific resources for parents of children with RTS include:

- Rubinstein-Taybi Syndrome: A Book for Families. Cathy, Stevens and Carey [1991]; available from Cathy Stevens, M.D.
- T.C. Thompson Children's Hospital 910 Blackford Street Chattanooga, TN. 37403 (423) 778-6112 RTS website: www.specialfriends.org RTS E-Mail List: zestes@sd69.bc.ca
- RTS website: www.rubinstein-taybi.org
- Rubinstein-Taybi Parent Group in the U.S.:
- Garry & Lorrie Baxter, RTS Parent Group, P.O. Box 146, Smith Center, KS 66967, 913-697-2984, 1-888-447-2989 (links to international groups on the website).

Assisting families in identifying community, state, and federal resources for financial, recreational, and adult/vocational considerations is important.

Siblings should have opportunities to be involved in support groups if interested.

Transition to Adulthood/Life Planning

Transition is a life-long process. Focus on maximizing independent functioning should occur throughout the lifespan.

A transition plan in the individualized education plan (IEP) is federally mandated in the U.S. The transition plan should be included in a child's IEP no later than 14 years of age.

Early referral to the local, regional, or state department of mental retardation and developmental disabilities can assist with transitions to independent living, semi-independent living, work opportunities, and integration into the community. The Bureau of Vocational Rehabilitation also assists with vocational planning and training after school age.

Transitioning to adulthood should take into consideration the following domains: education, health care, employment, community connections, income and government supports, and long-term home.

Assisting in the transition to providers of adult medical care should be accomplished with a clear communication of medical, emotional, behavioral, and social issues. It is important for adult providers to monitor typical conditions of aging, such as a decline in vision and hearing and intervene appropriately.

ACKNOWLEDGMENTS

We thank and extend our gracious appreciation to the following individuals for their review and professional guidance for these guidelines: Raouf Amin, M.D., Amal Assa'ad, M.D., William Ball, M.D., Lorrie Baxter, Ruthann Blough, Ph.D., Maria Callen, D.M.D., Robin Cottin, M.D., Kerry Crone, M.D., Michelle Farrell, Lisa Filipovich, M.D., Michael Gerber, M.D. Eric Gyuricsko, M.D., Tyler Harris, M.D., Fran Hickey, M.D., Molly Holland, MPH, R.D., Andrew Levitas, M.D. Anne Lucky, M.D., Charles Mehlman, D.O., Eugene Minevich, M.D., Karen Minning, Bonnie Patterson, M.D., Fred Petrij, M.D., John Romer, M.Ed., Mark Schapiro, M.D., Mark Shanon, Robert, Spicer, M.D., Frederic Strife, M.D., Theodore Striker, M.D., Ingrid Taff, M.D., Constance West, M.D., and Virchel Wood, M.D. The authors are grateful to The Special Friends Foundation for its generous support of this project.

REFERENCES

- Allanson J. 1990. Rubinstein-Taybi syndrome: The changing face. *Am J Med Genet Suppl* 6:38-41.
- Allanson J. 1993. Microcephaly in Rubinstein-Taybi syndrome. *Am J Med Genet* 46:244-246.
- Allanson J, Hennekam RCM. 1997. Rubinstein-Taybi syndrome: Objective evaluation of craniofacial structure. *Am J Med Genet* 71:414-419.
- American Academy of Pediatrics. 2000. Red Book 2000. Elk Grove Village, IL. pp 68, 3853, 435.
- Baker M. 1987. Dental and oral manifestations of Rubinstein-Taybi syndrome: Report of case. *J Dent Child* 54:369-371.
- Blough R., Petrij F., Dauwese J, Milatovich-Cherry A, Weiss L., Saal H., Rubinstein J. 2000. Variation in microdeletions of the cyclic AMP-responsive element-binding protein gene at chromosome band 16p13.3 in the Rubinstein-Taybi syndrome. *Am J Med Genet* 90:29-34.
- Bonioli E, Bellini C, Senes FM, Palmieri A, Di Stadio M, Pinelli G. 1993. Slipped capital femoral epiphysis associated with Rubinstein-Taybi syndrome. *Clin Genet* 44:79-81.
- Brei T, Burke M, Rubinstein J. 1995. Glaucoma and findings simulating glaucoma in the Rubinstein-Taybi syndrome. *J Pediatr Ophthalmol Strabismus* 32:248-252.
- Burke M. 1998. Ophthalmologic Findings in Rubinstein-Taybi Syndrome. Proceedings of the 1998 International Family Conference Rubinstein-Taybi Syndrome, Cincinnati, OH.
- Burton B, Kumar G, Bradford R. 1996. Granular cell tumour of the spinal cord in a patient with Rubinstein-Taybi syndrome. *Br J Neurosurg* 3:257-259.
- Callahan P. 2000. Undescended testis. *Pediatr Rev* 21:395.
- Cerqueiro-Mosquera J, Fleming A. 2000. The Bilobed flap: A new application in the reconstruction of congenital thumb deviation. *J Hand Surg* 25B 3:262-265.
- Critchley L, Gin T, Stuart J. 1995. Anesthesia in an infant with Rubinstein-Taybi syndrome. *Anesthesia* 50:37-38.
- Dajani A, Taubert K, Wilson W, Bolger A, Bayer A, Ferrieri P, Gewitz M, Shulman S, Nouri S, Newburger J, Hutto C, Pallasch T, Gage T, Levison M, Peter G, Zuccaro G. 1997. Prevention of bacterial endocarditis. Recommendations by the American Heart. *JAMA* 277: 1794.
- Ge N, Crandall B, Shuler J, Bateman J. 1995. Coloboma associated With Rubinstein-Taybi syndrome. *J Pediatr Ophthalmol Strabismus* 32:266-268.
- Gordeev V. 1977. Bronchial asthma with Rubinstein-Taybi syndrome in a child. *Pediatr* 11:72-73.
- Grunrow J. 1982. Gastroesophageal reflux in Rubinstein-Taybi syndrome. *J Ped Gastro Nutr* 1:273-274.
- Hennekam R, Van Doorne J. 1990. Oral aspects of Rubinstein-Taybi syndrome. *Am J Med Genet Suppl* 6:42-47.
- Hennekam R, Van Den Boogaard M, Sibbles B, Van Spijker H. 1990a. Rubinstein-Taybi syndrome in The Netherlands. *Am J Med Genet Suppl* 6:17-29.
- Hennekam R, Stevens C, Van de Kamp J. 1990. Etiology and recurrence risk in Rubinstein-Taybi syndrome. *Am J Med Genet Suppl* 6:56-64.
- Holland M. 1996. From a parent/nutritionist view: Nutrition and feeding issues for two special health needs. *Nutr Focus* 11:1-5.
- Kimura H, Ito Y, Koda Y, Hase Y. 1993. Rubinstein-Taybi syndrome with thymic hypoplasia. *Am J Med Genet* 46:293-296.
- Kinirons M. 1983. Oral aspects of Rubinstein-Taybi syndrome. *Br Dent J* 154:46-47.
- Lahlou B, Carrier C. 1971. Menometrorragies et bifidite uterine dans un cas du syndrome du "Pouce en Spatule" (Rubinstein et Taybi). *Rev Internationale de Pediatrie* 14:5-14.
- Levitas A, Reid C. 1998. Rubinstein-Taybi syndrome and psychiatric disorders. *J Intell Disabil Res* 42:284-292.
- Masuno M. 1998. Pilomatixomas in Rubinstein-Taybi syndrome. *Am J Med Genet* 77:81-82.
- Mehlman C. Pediatric hip disorders associated with Rubinstein-Taybi syndrome (abstract in submission). International Family Conference on Rubinstein-Taybi Syndrome.
- Mehlman C, Rubinstein J, Roy D. 1998. Instability of the patellofemoral joint in Rubinstein-Taybi syndrome. *J Pediatr Orthop* 18:508-511.
- Miller R, Rubinstein J. 1995. Tumors in Rubinstein-Taybi syndrome. *Am J Med Genet* 56:112-115.
- Moe J, Holland M, Johnson R. 1998. Breastfeeding practices of infants with Rubinstein-Taybi syndrome. *J Hum Lactation* 14:311-315.
- Olsen D, Keonig R. 1997. Thyroid function in Rubinstein-Taybi syndrome. *J Clin Endo and Metab* 83:3264-3266.
- Petrij F, Dauwese H, Blough R, Giles R, van der Smagt J, Wallerstein R, Maaswinkel-Mooy P, van Karnebeek C, van Ommen G, van Haeringen A, Rubinstein J, Saal H, Hennekam R, Peters D, Brueuning M. 2000. Diagnostic analysis of the Rubinstein-Taybi syndrome: Five cosmids should be used for microdeletion detection and low number of protein truncating mutations. *J Med Genet* 37:168-176.
- Rivas R, Fragoso R, Ramos-Zepeda G, Vaca A, Hernandez G, Gonzalez-Quiroga G, Olivares N, Cantu J. 1980. Deficient cell immunity and mild intermittent hyperaminoacidemia in a patient with the Rubinstein-Taybi syndrome. *Acta Paediatr Scand* 69:123-125.
- Roberts KB. 1996. Gastroesophageal reflux in infants and children who have neurodevelopment disabilities. *Pediatr Rev* 17:211-212.
- Rosenbaum K, Johnson D, Fitz C, McCullough D. 1990. Tethered cord in Rubinstein-Taybi syndrome. *Am J Hum Genet Suppl* 47:A75.
- Roy F, Summitt R, Hiatt R, Hughes J. 1968. Ocular manifestations of the Rubinstein-Taybi syndrome. *Arch Ophthal* 79:272-278.
- Rubinstein J. 1990. Broad thumb-hallux (Rubinstein-Taybi) syndrome 1957-1988. *Am J Med Genet Suppl* 6:3-16.
- Sashi V, Fryburg J. 1995. Vascular ring leading to tracheoesophageal compression in a patient with Rubinstein-Taybi syndrome. *Clin Genet* 48:324-327.

- Scott A, Proops D, Kunick T. 2000. Post-cricoid web associated with Rubinstein-Taybi syndrome. *J Laryng Otol* 114:637–638.
- Siraganian P, Rubinstein J, Miller R. 1989. Keloids and neoplasms in the Rubinstein-Taybi syndrome. *Med Pediatr Oncol* 17:485–491.
- Skousen F, Wardinsky R, Chenaille P. 1996. Medulloblastoma in patient with Rubinstein-Taybi syndrome. *Am J Med Genet* 66:367.
- Stevens C. 1997. Patellar dislocation in Rubinstein-Taybi syndrome. *Am J Med Genet* 72:188–190.
- Stevens C, Bhakta M. 1995. Cardiac abnormalities in the Rubinstein-Taybi syndrome. *Am J Med Genet* 59:346–348.
- Stevens C, Carey J. 1991. Rubinstein-Taybi syndrome: A book for families. T.C. Children's Thompson Children's Hospital, TN.
- Stevens C, Carey J, Blackburn B. 1990a. Rubinstein-Taybi syndrome: A natural history study. *Am J Med Genet Suppl* 6:30–37.
- Stevens C, Hennekam R, Blackburn B. 1990b. Growth in the Rubinstein-Taybi syndrome. *Am J Med Genet Suppl* 6:51–55.
- Stevens C, Schmitt C, Speraw S. 1999. Behavior in Rubinstein-Taybi syndrome. *Proceedings of the Greenwood Genetic Center* 18:144–145.
- Stirt M. 1981. Anesthetic problems in Rubinstein-Taybi syndrome. *Anesth Analg* 60:534–536.
- Stirt J. 1982. Succinylcholine in Rubinstein-Taybi. Syndrome. *Anesthesiology* 57:429.
- Surdulescu V, Amin R, Rubinstein J, Loggie J. Breathing-related sleep disorders and hypertension in patients with Rubinstein-Taybi syndrome (abstract). International Family Conference on Rubinstein-Taybi Syndrome. Cincinnati, OH.
- Taff I, Madad S. 1998. Behavioral characteristics of patients with Rubinstein-Taybi syndrome (poster session). International Family Conference on Rubinstein-Taybi Syndrome. Cincinnati, OH.
- Tanphaichitr P, Mekanandha V, Kotchbhakdi N. 1979. A case of Rubinstein-Taybi syndrome associated with Nephrotic syndrome. *J Med Ass Thailand* 62:44–46.
- Taylor T, Callen M. 1999. Rubinstein-Taybi syndrome: A summary of oral and perioral findings (abstract). International Family Conference on Rubinstein-Taybi Syndrome. Cincinnati, OH.
- Villella A, Bialostocky D, Lori E, Meyerson H, Hostoffer R. 2000. Rubinstein-Taybi syndrome with humoral and cellular defects: A case report. *Archives of Disease in Childhood* 83:360–361.
- Wallerstein R, Anderson C, Hay B, Gupta P, Gibas L, Ansari K, Cowchock S, Weinblatt V, Reid C, Levitas A, Jackson L. 1997. Submicroscopic deletions at 16p13.3 in Rubinstein-Taybi syndrome: Frequency and clinical manifestations in a North American population. *J Med Genet* 34:203–206.
- Wood V, Rubinstein J. 1987. Surgical treatment of the thumb in the Rubinstein-Taybi syndrome. *J Hand Surg* 12:166–172.
- Wood V, Rubinstein J. 1999. Duplicated longitudinal bracketed epiphysis “Kissing delta phalanx” in Rubinstein-Taybi syndrome. *J Ped Ortho* 19:603–606.
- Wyatt D. 1990. Transient hypoglycemia with hyperinsulinemia in a newborn infant with Rubinstein-Taybi syndrome. *Am J med Genet* 37:103–105.
- Zucconi M, Ferini-Strambi L, Erminio C, Pestalozza G, Smirne S. 1993. Obstructive sleep apnea in the Rubinstein-Taybi syndrome. *Respiration* 60:127–132.