Phenotype and Natural History in Marshall–Smith Syndrome

Shaw, Adam C.; van Balkom, Inge D.C.; Bauer, Mislen; Cole, Trevor R.P.; Delrue, Marie-Ange; Van Haeringen, Arie; Holmberg, Eva; Knight, Samantha J.L.; Mortier, Geert; Nampoothiri, Sheela; ...

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Phenotype and Natural History in Marshall–Smith Syndrome

Adam C. Shaw,[1]* Inge D.C. van Balkom,[2,3] Mislen Bauer,[4] Trevor R.P. Cole,[5] Marie-Ange Delrue,[6] Arie Van Haeringen,[7] Eva Holmberg,[8] Samantha J.L. Knight,[9] Geert Mortier,[10] Sheela Nampoothiri,[11] Silvija Pušeljić,[12] Martin Zenker,[13] Valerie Cormier-Daire,[14] and Raoul C.M. Hennekam[15]

[1]Clinical and Molecular Genetics Unit, UCL Institute of Child Health, London, UK

[2]Jonx Department of Youth Mental Health, Lentis Psychiatric Institute, Zuidlaren, The Netherlands

[3]Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands

[4]Department of Clinical Genetics, Miami Children's Hospital, Miami, Florida

[5]Clinical Genetics Unit, Birmingham Women's Hospital, Birmingham, UK

[6]Service de Génétique Médicale, CHU de Bordeaux, Université Bordeaux 2, Bordeaux, France

[7]Department of Clinical Genetics, LUMC, Leiden, The Netherlands

[8]Department of Medical Genetics, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway

[9]NIHR Biomedical Research Centre, Oxford and Wellcome Trust Centre for Human Genetics, Oxford, UK

[10]Center for Medical Genetics, Antwerp University Hospital, Antwerp, Belgium

[11]Department of Pediatric Genetics, Amrita Institute of Medical Sciences and Research Center, Cochin, Kerala, India

[12]Pediatrics Clinic, Clinical Hospital Centre Osijek, Osijek, Croatia

[13]Institute of Human Genetics, University Hospital of Magdeburg, Magdeburg, Germany

[14]Department of Genetics and INSERM, Hôpital Necker Enfants Malades, Paris, France

[15]Department of Pediatrics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Received 11 June 2010; Accepted 16 August 2010

Marshall–Smith syndrome (MSS) is a distinctive entity of unknown etiology with fewer than 50 patients described in the medical literature to date. Through an International collaboration and use of an online wiki to facilitate data collection and sharing, we further delineate the phenotype and natural history of this syndrome. We present 15 new patients, the oldest being 30 years, provide an update on four previously published cases, and compare all patients with other patients reported in literature. Main clinical features are moderate to severe developmental delay with absent or limited speech, unusual behavior, dysharmonic bone maturation, respiratory compromise secondary to upper airway obstruction, short stature, and kyphoscoliosis. Facial features are characteristic with high forehead, underdeveloped midface, proptosis, anteverted nares, and everted lips. Minor abnormalities of brain morphology such as hypoplasia of the corpus callosum are common. Mortality from respiratory complications is high, but airway support increasingly allows survival into adulthood. Array-CGH was performed on 12 of the cohort and no copy number variants of clear clinical relevance were identified. The present study is the first reported use of an online wiki to aid delineation of a genetic syndrome, and illustrates its value in collecting detailed data in rare conditions.

How to Cite this Article:
Shaw AC, IDC van Balkom, Bauer M, Cole TRP, Delrue M-A, Van Haeringen A, Holmberg E, Knight SJL, Mortier G, Nampoothiri S, Pušeljić S, Zenker M, Cormier-Daire V, Hennekam RCM. 2010. Phenotype and natural history in Marshall–Smith syndrome.
Am J Med Genet Part A 152A:2714–2726.

Key words: Marshall–Smith syndrome; mental retardation; dysostosis; kyphoscoliosis; natural history; wiki

*Correspondence to:
Adam C. Shaw, BM, M.D., Clinical and Molecular Genetics Unit, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK.
E-mail: a.shaw@ich.ucl.ac.uk

Published online 8 October 2010 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.33709

INTRODUCTION

In 1971, the physicians R.E. Marshall, C.B. Graham, C.R. Scott, and D.W. Smith reported two unrelated male infants with unusual facial features, failure to thrive, developmental delay, and what was described as marked early acceleration of osseous maturation [Marshall et al., 1971]. The facial appearance was very similar in both and characterized by prominent eyes, thick eyebrows, depressed nasal bridge, and a small upturned nose with prominent nares. Both patients had respiratory difficulties, and one of them had died at 20 months of age. To date, at least 43 cases with this phenotype have been described in the literature, and the entity has become known as the Marshall–Smith syndrome (MSS). The majority of reported cases died in infancy or early childhood, but prolonged survival of some cases especially due to improved management of the respiratory difficulties, suggested such early demise is not inevitable.

The majority of previous reports have been of single patients, with the largest published series comprising 5 new cases [Adam et al., 2005], collated through an international collaboration. Meaningful study of ultra-rare phenotypes such as MSS, necessitates large-scale collaboration between clinicians. The apparent difficulty in amassing sizable cohorts to date may be compounded by inefficient means of effective data sharing, inconsistent data-sets, and difficulty tracing patients who are not under active follow-up. The use of evolving web-based data sharing methods such as a wiki, may provide a solution to some of these problems and aid delineation of rare phenotypes. Wikis are easy-to-use text-based data repositories that can be accessed through a web browser and allow any individual with world-wide-web access to read the content and add their own text. Wikis may be open-access or available only to registered users and can easily be created using a number of free open-source or commercial software products.

Here we provide the phenotype and natural history of 15 new and 4 previously published patients on whom data were in-part collected and shared using a secure online wiki resource. Three patients are aged over 16 years and allow us to further describe the adult phenotype of MSS.

METHODS

A literature search was performed using "Marshall–Smith" as search term. The reference lists of all manuscripts thus retrieved were searched manually for further reports.

Patients were referred to us by colleagues around the world and through the international Marshall–Smith Support group. All patients referred have been personally evaluated by at least one of the authors. In addition to medical assessment and clinical examination, personal history and additional information on the patients were assimilated using an online wiki. An early draft of this paper consisting of the general description of the syndrome and medical complications, was re-written in lay language and translated into French, German, Dutch, Norwegian, Portuguese, Spanish, and Croatian. The translated text was uploaded to a secure wiki website, accessible to registered clinicians and members of the International MSS patient support group (www.marshallsmith.org). Families were encouraged to read the text and add their own data and comments.

Agilent Technologies 244 K genome-wide arrays were used for the patient testing. In brief, genomic DNA from the patient and from a single sex-matched reference were double-digested using the restriction endonucleases *Alu*I and *Rsa*I (Promega, Wisconsin) and purified using Microcon centrifugal filter devices (Millipore Corporation, Massachusetts). 1.5 μg of the digested products were differentially labeled by random priming with Cy3-dUTP and Cy5-dUTP (Perkin Elmer, Massachusetts) and co-hybridized to the arrays for 48 hr at 65°C in a rotating oven (Agilent Technologies, Inc., Illinois). Hybridized arrays were washed according to Agilent Technologies, Inc. protocols (www.agilent.co.uk) with the exception that the final stabilization step was not performed. Hybridized arrays were scanned at 5 μM resolution immediately following washing using an Agilent DNA Microarray Scanner. Image data were extracted using Agilent Feature Extraction software version 8.5 and analyzed using Agilent CGH Analytics software version 3.4 (z-score method setting). Potential genome imbalances were recorded if 4 or more consecutive oligonucleotide probes gave values that fell outside the log10 Cy-dye threshold ratios. This gave an average resolution of ~40 kb. The positions of proximal and distal oligonucleotides showing potential imbalances were noted and the regions queried both in the Database of Genomic Variants [Iafrate et al., 2004] and the laboratory's own database. Approval from the NHS (UK) National Research Ethics Service was obtained prior to the study commencement.

RESULTS

Clinical data on all patients are summarized in Table I, and patients 1–18 are illustrated in Figure 1. A detailed description of the oldest patient, aged 30, is provided below and she is illustrated in Figure 2. Four patients have been previously in the medical literature: Patient 13 [Deshpande et al., 2006], Patient 14 [Adam et al., 2005], Patient 15 [Dernedde et al., 1998], and Patient 17 [Williams et al., 1997].

Mean maternal age at birth was 29.3 years, and mean paternal age at birth was 33.2 years. The mean parental ages for normal populations vary year by year and by country. Although comparison of the parental age for each patient with published data on mean paternal and maternal age for the corresponding year of birth is difficult due to the varying countries of origin, it is unlikely that these data are significantly deviated from the mean, suggesting no parental age effect in the cohort. Mean birth weight for term deliveries was 2,936 g for males and 3,229 g for females. Mean and median times to conception were 5 and 1 month, respectively.

Respiratory problems were present in 14 patients. The majority presented at birth or shortly after with upper airway obstruction or apneas. Laryngomalacia was not uncommon (four subjects), but in most patients the obstruction appeared secondary to the combined changes to craniofacial anatomy, where retrognathia, an underdeveloped midface, narrow choanae, and anteriorly placed larynx reduced airway patency. Treatment was by tracheostomy in five subjects, nasopharyngeal airway in six subjects and positive pressure ventilation in one patient. In two individuals, surgery was performed to relieve the obstruction. Obstructive sleep apnea was common in older children and adults (nine subjects) including those who did not experience respiratory problems in infancy (two patients).

Spastic quadraparesis presented in the first year of life in two patients, secondary to dysplasia of the upper cervical vertebrae.

TABLE I. Clinical Characteristics of Present 19 Patients With Marshall–Smith Syndrome

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
Epidemiology																				
Gender	M	F	F	M	M	F	F	F	F	M	M	F	F	F	M	M	F	M	F	8 M/11 F
Age	3 wk[a]	6 m	6 m	26 m	3 y	5 y	7 y	7 y	7 y	7 y	8 y	8 y	8 y	14 y	13 y	14 y[a]	16 y	21 y	30 y	3 w to 30 y
Mat/Pat age (yr)	26/28	36/37	18/23	22/32	30/31	24/32	23/31	32/36	32/51	27/29	24/31	34/32	20/21	33/40	35/33	26/32	28/28	38/39	27/27	
Growth																				
Birth weight (g)	2,600	3,400	3,570	2,950	2,975	2,170		1,590	4,030	3,230	2,400	2,183	3,630	2,990	2,000	2,270	2,800	3,860	2,977	
Gestation	Term	Term	Term	Term	Term	36 wk	31 wk	32 wk	41 wk	Term	35 wk	Term	Term	Term	Term	34 wks	Term	Term	Term	
Weight (kg)	2.97	5		9.1	15	13.8	18		17	21	28	14.5		30	22	19	35	41	32	
Height (cm)	55	68		82	100	107	118	103	120	120	136	100		138	120	122	131		127	
Height centile (SDS if centile < 2)	75	64		3	10	10	20	7	38	30	72	<0.4 (−4.95)	85	0.2 (−2.90)	<0.4 (−4.9)	<0.4 (−5.6)	<0.4 (−4.6)	<0.4 (−6)	<0.4 (<−6)	
Development																				
Degree of delay	N/A	N/A	N/A	Sev	Mod	Mod-Sev	Mod-Sev	Mod	Mod-Sev	Mod	Mod	Sev	Mod	Mod	Sev	Mod-Sev	Sev	Sev	Mod-Sev	
Walked	N/A	N/A	N/A	–	–	–		–	–	3 y	3 y	–	2 y	4.5 y	Never	Never	Never	Never	9 y	
First words	N/A	N/A	N/A	–	–	60 m		60 m	42 m	36 m	–	–	–	48 m	None	None	None	None	10 y	
Craniofacial features																				
High forehead	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Proptosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Underdeveloped midface	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	18/19
Short nose	+	+	+	+	+	–	–	–	+	+	–	+	+	+	+	+	+	+	+	15/19
Anteverted nares	+	+	+	+	+	–	+	–	+	+	–	+	–	+	–	+	–	–	–	11/19
Prominent premaxilla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Short philtrum	+	–	–	–	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	13/19
Everted lips	–	–	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	13/19
Irregular dentition	N/A	N/A	N/A		+	–		–	–	+	+	–	–	+	+	+	+	–	+	8/14
Gum hypertrophy	–	+		+	+	–		–	–	+	–	–	–	+	+	+	–	–	–	7/17
Retrognathia	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	17/19
Low-set ears	–	–		+	+	+	+	–	–	+	+	+	–	–	+	+	+	–	–	10//18
Eyes																				
Myopia	–	–		–	−14	−2.5	−6/−5	−12/−9	−2/−7	–	−2	−8	–	–	+	−7/−8	–	–	–	9/18
Blue sclerae	+	+	+	+	+	+	+	–	+	+	–	+	–	–	+	+	+	+	+	15/19
Glaucoma	–	–		–	+	+		–	–	–	–	–	–	–	+	–	–	–	–	3/17
Optic nerve hypoplasia	–	–		+	–	–		–	–	–	–	+	+	–	–	+	+	–		5/16
Respiratory																				
Choanal stenosis	–	+	+	–	–	+		–	–	+	–	–	–	+	+	–	–	–	–	6/18

(Continued)

TABLE I. (*Continued*)

Respiratory problems	+	+	+	−	+	+	+	−	−	+	−	+	+	+	+	+	−	+	+	14/19
Obs sleep apnea	N/A	−		−	+	+	−	−	+	+	+	N/A (trach)	+	+	+	N/A (trach)	−	+	−	9/15
Neurology																				
High tone	−	−		−	−	−		−	−	−	−		−	+	+		+	+	−	4/15
Brisk reflexes	−	−		−	−	−		−	−	−	−		+	+	+		+	+	−	5/15
Cervical cord compression	−	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	2/19
Brain MRI		Pachygyria hypoplasia callosal body	Small cerebellum	CT scan: N	Hypoplasia callosal body	Delayed myelination		N	N	N	Hypoplasia callosal body	Hypoplasia callosal body	N	N	N	Dilated cerebral ventricles	Dilated cerebral ventricles		N	
Skeletal																				
Abnormal bone maturation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Craniosynostosis	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	1/19
Bone fractures	−	−	−	−	1	−	−	−	4	4	1	−	−	−	−	−	−	−	−	4/19
Kyphoscoliosis	−	−	−	−	−	+	+	−	−	+	−	+	−	+	+	+	+	+	+	10/19
Other																				
Cardiac defect	−	−		−	−	−		VSD	−	−	−	−	−	−	−	−	VSD	−	−	2/17
Pulmonary hypertension	−	−		−	−	−		−	−	−	−	−	−	−	−	+	−	−	−	1/17
Hearing loss	+	+		−	+	+	−	−	+	+	−	−	−	−	+	+	+	−	−	9/18
Umbilical hernia	−	+		−	−	−		−	−	+	−	−	−	−	−	−	−	−	−	2/17
Cryptorchidism	−	N/A	N/A	−	+	N/A	N/A	N/A	N/A	−	+	N/A	N/A	N/A	−	+	N/A	−	N/A	3/8
Hypertrichosis	−	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	16/19
Fetal finger pads	+	−		+	+	+		+	+	−			−	+	−		−	+	−	8/14
Miscellaneous		IgA deficiency vesico-ureteral reflux		Abnormal pinnae	Hypospadias					Anteriorly placed anus; pyloric stenosis		Choroid plexus cyst antenatly; tethered spinal cord		Vascular skin naevus	Pyloric stenosis	No secondary dentition	Wilms tumour aged 4			

Fields are left blank if no data on a feature are available. M, male; F, female; N/A, not applicable; sev, severe; mod, moderate; N, normal; SDS, standard deviation score; d, day; w, week; m, month, y, year.

[a]Deceased.

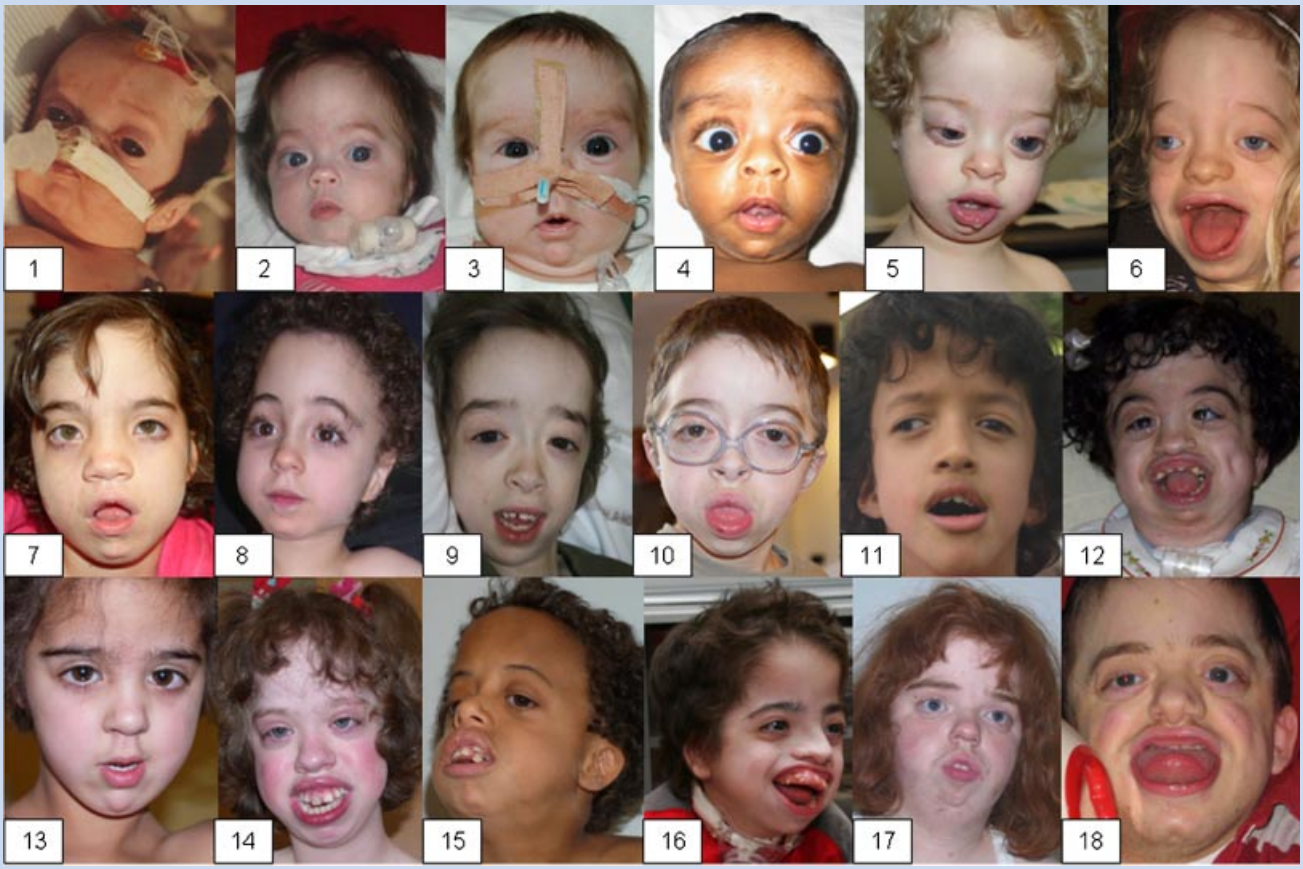

FIG. 1. Facial pictures of the presented patients with Marshall–Smith syndrome. Patients are identified by their number in the figure. Age at imaging is as follows: Patient 1, 2 weeks; Patient 2, 6 months; Patient 3, 3 months; Patient 4, 2 years; Patient 5, 20 months; Patient 6, 4 years; Patient 7, 6 years; Patient 8, 5 years; Patient 9, 5 years; Patient 10, 6 years; Patient 11, 8 years; Patient 12, 7 years; Patient 13, 6 years; Patient 14, 12 years; Patient 15, 13 years; Patient 16, 13 years; Patient 17, 16 years; Patient 18, 20 years. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

FIG. 2. Changing phenotype over time in patient 19 from 3 weeks to 30 years. Age at imaging is shown in the figure (w, weeks; m, months; y, years). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

Both patients recovered fully following cervicomedullary decompression. Patient 14 had asymptomatic narrowing of the cervical spine noted on imaging performed as surveillance. Corneal scarring occurred peri-operatively in three patients secondary to proptosis and incomplete eye closure. All subjects had moderate to severe mental retardation with limited or absent speech. Parents frequently reported a strong attachment to a favorite toy which remained for years. More detailed evaluation of the neurocognitive profile will be presented elsewhere [van Balkom et al., unpublished work].

CLINICAL REPORT

This 30-year-old woman was diagnosed with MSS at age 2 months. There were no antenatal concerns and she breathed spontaneously at birth with no airway support required. She had feeding difficulties in the neonatal period with a weak suck, taking over an hour to complete a feed. She developed upper respiratory tract obstruction as an infant and eventually required an emergency tracheostomy at 13 months. Her feeding problems and neurocognitive development improved substantially afterwards. The tracheostomy remained in place until 4 years and there have been no further respiratory problems since. Menarche occurred at 14 years and was normal. She had a single seizure at the age of 6. She had very narrow ear canals and had a canaloplasty aged 8 years. Facial hirsutism became marked aged 16, and has been successfully treated with laser removal. She walked unaided from 9 years on but in the last years her mobility reduced and she developed severe osteoarthritis. She was continent from the age of 3. Her first words were at 10 years, but she had only 3 or 4 words in total. She communicated well through pointing and leading the way. She was a happy and sociable lady who enjoyed music, visiting family and shops. Linear growth was normal in childhood, but stopped growing at around 13 years. She lost height due to scoliosis and current adult height is 127 cm. Bone age at 2 months was approximately 4 years, and at 8 chronological years was 10 years.

She had always typical facial features (Fig. 2). Her eyebrows and eyelashes were particularly thickened and coarse. She had a wide mouth, protruding tongue, irregular teeth, and everted, prominent lips, and depressed nasal bridge. She had a soft, supple skin with hypertrichosis on areas that have not received depilatory treatment. She had a scoliosis of 60 degrees, marked thoracic kyphosis, and a cautious gait with externally rotated hips. Her muscle tone was high and she had strong power. She appeared shy with gaze avoidance, but smiled, laughed and enjoyed company.

ARRAY-CGH RESULTS

Genomic DNA samples from Patients 1, 3, 5, 6, 7, 8, 10, 13, 14, 15, 17, and 18 were available for aCGH testing. For patients 3, 5, 6, 7, 10, 13, 14, 15, and 17 only genome imbalances/CNVs that have been noted in the Database of Genomic Variants (DGV) (http://projects.tcag.ca/variation/), or observed many times in our own sample sets, were identified. In patients 1, 8, and 18, several putative genomic imbalances were identified, but follow-up studies using a combination of FISH, MLPA, and study of parental samples, suggested none of the changes were likely to be of clinical significance.

DISCUSSION

We found 43 patients with MSS or a very similar phenotype described in the literature [Marshall et al., 1971; Nabrady and Bozalyi, 1973; Tipton et al., 1973; Visveshwara et al., 1974; De Toni et al., 1976; Hassan et al., 1976; Perrin et al., 1976; Iafusco et al., 1977; Ferran et al., 1978; Flatz and Natzschka, 1978; LaPenna and Folger, 1982; Johnson et al., 1983; Menguy et al., 1986; Roodhooft et al., 1988; Yoder et al., 1988; Smyth et al., 1989; Charon et al., 1990; Eich et al., 1991; Pappas and Rekate, 1991; Sperli et al., 1993; Sharma et al., 1994; Endo et al., 1995; Cullen et al., 1997; Williams et al., 1997; Antila et al., 1998; Chatel et al., 1998; Dernedde et al., 1998; Seidahmed et al., 1999; Summers et al., 1999; Moon et al., 2002; Sumiya et al., 2002; Wang, 2002; Diab et al., 2003; Watanabe et al., 2003; Butler, 2004; Adam et al., 2005; Deshpande et al., 2006; Travan et al., 2008]. A summary of the major manifestations of 39 published cases (excluding the 4 that have been updated here) is shown in Table II. We have excluded five possible cases due to difficulty interpreting language or insufficient information to confirm the diagnosis [de la Torre Cecilia et al., 1989; Moon et al., 2002; Watanabe et al., 2003; Kubota et al., 2005; Mandim et al., 2007]. Some additional cases cited in the literature are likely to have alternative diagnoses such as Marshall–Stickler syndrome [Cooley et al., 2004] and Weaver syndrome [Jalaguier et al., 1983].

The major manifestations of MSS from patients described in the literature and the present studied cohort are summarized in Table III. Features described in most patients are the moderate to severe developmental delay, severe respiratory difficulties, distinctive facial features (high forehead; proptosis; anterverted nares; retrognathia), abnormal bone ossification, and failure to thrive. We consider these findings, in particular the abnormal radiographs, required to make the diagnosis. Other highly prevalent features are blue sclerae, hypertrichosis, gingival hypertrophy, and the development of kyphoscoliosis in later childhood and adolescence. The six oldest individuals in the cohort (aged over 13 years) and one 8-year-old had short stature (SDS < -2.0) suggesting this is also a consistent feature of the adult phenotype, compounded by kyphoscoliosis.

Facial Morphology

The typical facial phenotype consists of a high and prominent forehead, shallow orbits, flat midface, prominent premaxilla, and small and retracted mandible. The nose is frequently short, with upturned tip and anteverted nares, the philtrum may be long in infancy but in time may become short and everted. In older children the lips are frequently full and everted making the gingival hypertrophy and markedly irregularly placed teeth well visible in most patients. Two of the adult patients had a protruding tongue, but it is uncertain whether this is a frequent feature of the adult phenotype. The ears may be low set and minor anomalies of morphology are common. Facial hair is normal, including secondary hair in males.

Ophthalmology

The eyes are large and the orbits shallow, which both contribute to the proptosis. High myopia is present but glasses are frequently not tolerated which impairs visual development. Glaucoma, when

TABLE II. Major Characteristics of 39 Patients With Marshall–Smith Syndrome From Literature Compared to a Summary of the Present Series

	Marshall et al. [1971] #1	Marshall et al. [1971] #2	Nabrady and Bozalyi [1973]	Tipton et al. [1973]	Visveshwara et al. [1974]	De Toni et al. [1976]	Hassan et al. [1976]	Perrin et al. [1976]	Iafusco et al. [1977]	Ferran et al. [1978]	Flatz and Natzschka [1978]	LaPenna and Folger [1982]	Johnson et al. [1983] #1	Johnson et al. [1983] #2	Menguy et al. [1986]	Roodhooft et al. [1988]	Yoder et al. [1988]	Smyth et al. [1989]	Charon et al. [1990]	Eich et al. [1991] #1	Eich et al. [1991] #2
Epidemiology																					
Gender	M	M	M	F	M	M	F	M	F	M	F	F	M	F	F	F	F	F	F	M	F
Age	20 m[a]	10 m	8 m	13 d[a]	3 m[a]	3 y	10 wk[a]	6 m[a]	7 d[a]	4 wk[a]	18 d[a]	2 y	2 m[a]	16 m[a]	7 d	4 y	3 m[a]	2 y	7 wk[a]	7 wk[a]	3 y[a]
Growth																					
Birth weight (g)	3,300	4,500	3,800	2,595	2,468	3,580	3,800	3,100	2,500	3,900	2,450	2,950	2,400	1,750	2,490	3,850	3,420		2,530	3,400	3,710
Gestation (wk)	Term	Term	Term		Term	Term	Term	Term	42	45	Term	Term	35	34	Term	Term	Term	Term	34	Term	Term
Failure to thrive	+	+			+	+		+		−		+	+	+		+	+	+	+	+	+
Psychomotor delay	+	+	+			+		+				+		+		+		+	+		+
Craniofacial features																					
High forehead	+	+	+	+	+	+	+	+	−	+	+		+	+	+		+	+	+	+	
Proptosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	
Short nose	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	
Anteverted nares	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	
Prominent premaxilla	+	+	+	−	+	+	+	−	+		−		+	+	+	+	−	+	+	+	
Short philtrum	−	−	−	−	−	−	−	−	−		−		−	−	−		−	−	−	−	
Retrognathia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eyes																					
Blue sclerae	+	+	+			+		−			+		+	+			+	+			
Glaucoma					−			−								−		−	−		
Respiratory problems	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	
Callosal body underdevelopment	−							−					−	−		−	−		−	−	−
Skeletal																					
Abnormal bone maturation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Craniosynostosis				−	−		−	+		−			+	−		−	−	−	−	−	−
Kyphoscoliosis	+	+		−			−	−					−	−			−		−	−	−
Bone fractures				−			−	−					−	−					−		−
Cardiac defect	−	−		PDA			ASD	PDA		−		−	−	PDA	−	−	−	−	−	−	
Umbilical hernia	+	+	+		+	−	+	−					−		−						
Hearing loss													+					−	−		+
Hypertrichosis	−	−			+	−	+	+	+		+	+	+						+		

(Continued)

TABLE II. (*Continued*)

	Eich et al. [1991] #3	Pappas and Rekate [1991]	Sperli et al. [1993]	Sharma et al. [1994]	Endo et al. [1995]	Cullen et al. [1997]	Antila et al. [1998]	Chatel et al. [1998]	Seidahmed et al. [1999]	Summers et al. [1999]/Butler [2004]	Sumiya et al. [2002]	Wang [2002]	Diab et al. [2003]	Adam et al. [2005] #1	Adam et al. [2005] #2	Adam et al. [2005] #4	Adam et al. [2005] #5	Travan et al. [2008]	Total literature	Total current cases
Epidemiology																				
Gender	M	M	M	F	F	F	M	F	F	M	F	M	F	F	M	M	M	F	18 M/21 F	8 M/11 F
Age	1 d[a]	2 y	5 y	2 m[a]	8 m	5 m[a]	7 m	1 d[a]	4 m[a]	4 y	7 y	6 y	7 y	2 y	19 y[a]	2 y	2 y	16 d[a]	1 d–19 y	3 wk to 30 y
Growth																				
Birth weight (g)	2,300		3,780	3,200	2,500	2,760	3,890	2,150	2,400	3,060	2,680	2,850	2,255	3,250	3,100	3,400		2,250	Term mean 3,144	Term mean 3,085
Gestation (wk)	Term		Term	Term	36	Term	Term	33	Term	Term	Term	Term	36	Term		37		Term		
Failure to thrive			+	+	+					+	+	+	+		+		+	+	24/25	14/14
Psychomotor delay		+	+		+				+	+	+	+	+	+	+	+	+		23/23	16/16
Craniofacial features																				
High forehead		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34/35	19/19
Proptosis	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36/37	19/19
Short nose	+	+	+	–	+	+	+		+	+			+					+	28/31	15/19
Anteverted nares			+		+	+	+	+	+	+	+	+	+	+	+	+		+	33/34	11/19
Prominent premaxilla			+			+	+					+	+						19/23	19/19
Short philtrum			+	–		–	–			+		+	+				+		5/25	13/19
Retrognathia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	38/38	17/19
Eyes																				
Blue sclerae			+	+	+		+	–	+	–	+		+	+	+		+		19/22	15/19
Glaucoma												+	+						2/7	3/17
Respiratory problems	+		–	+	+	+	+	+	+	+	+	+		+	+	–	+	+	32/36	14/19
Callosal body underdevelopment	–		+		+			–	+	–	–	–	–	–	–	–	–	+	4/23	4/16
Skeletal																				
Abnormal bone maturation	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38/38	19/19
Craniosynostosis	–		–		–	–				+	+								4/19	1/19
Kyphoscoliosis	–					–				+	+			+	+		+		7/18	10/19
Bone fractures		2			–	–				2			15	4					4/13	4/19
Cardiac defect	–				–			–											4/18	2/17
Umbilical hernia			–		–		+	+		–	+								8/15	2/17
Hearing loss											+	+		+	+				6/8	9/17
Hypertrichosis			+		+			+	+	+	+								14/17	15/18

Data are indicated only if a feature was stated positive or negative in the article or clearly visible in the figures.

[a]Deceased.

TABLE III. Most Common Manifestations of Marshall–Smith Syndrome

Manifestation	Literature (n = 39)	Present study (n = 19)	Total
Dysharmonic bone maturation	100%	100%	100%
Psychomotor delay	100%	100%	100%
Typical facial appearance[a]	100%	100%	100%
Failure to thrive	96%	100%	97%
Respiratory problems	89%	74%	84%
Blue sclerae	86%	79%	83%
Hypertrichosis	82%	83%	83%
Kyphoscoliosis	39%	53%	46%
Gum hypertrophy	—	41%	41%
Umbilical hernia	53%	12%	31%
Cardiac defect	22%	12%	17%

[a]High forehead, proptosis, underdeveloped midface, anteverted nares, and retrognathia.

present, is due to congenital anomalies of morphology of the anterior chamber or trabecular meshwork and affects about 30% of patients. Optic nerve hypoplasia has been found in some with glaucoma, but also in absence of glaucoma suggesting it to be a primary phenomenon. Several patients experienced corneal ulceration peri-operatively due to incomplete eye closure, and this should be highlighted as a preventable complication. Patients should have regular ophthalmologic evaluation due to the range of pathologies, the difficulty of patients to self-report symptoms, and the importance of early intervention to reduce secondary phenomena.

Respiratory Complications

The frequent and significant respiratory difficulties in MSS result from a combination of pathologies, mainly upper airway obstruction (retrognathia; choanal stenosis; abnormal larynx), and aspiration pneumonia (secondary to underdeveloped epiglottis and pharyngeal incoordination). Retrognathia is a frequent sign in MSS and contributes to both upper airway obstruction and poor visualization of the anatomy on laryngoscopy. Choanal stenosis occurred in six of our cohort and in four additional cases from literature [Tipton et al., 1973; Visveshwara et al., 1974; Flatz and Natzschka, 1978; Summers et al., 1999] suggesting an incidence of 5–10%. It presents later than classical choanal atresia, and other cases have been reported with partial stenosis making passage of feeding tubes difficult [Perrin et al., 1976; Menguy et al., 1986] suggesting that the stenosis features a spectrum of expression and is possibly caused by midface underdevelopment. Analysis of the laryngeal features in MSS is hampered by the variety of terms used to describe similar findings such as laryngomalacia, laryngeal stenosis, glottic stenosis, anteriorly placed larynx, and rudimentary epiglottis. In some patients, the larynx is described as anatomically normal, but with a functional obstruction. Irrespective of the cause the upper airway obstruction leads to an increase in negative thoracic inspiratory pressure, increasing the risks of aspiration and increasing pulmonary venous return contributing to increased pulmonary vascular pressure. Pulmonary hypertension with evidence of right ventricular hypertrophy has been reported in four cases in the literature and one of our series, and has a poor prognosis [LaPenna and Folger, 1982; Johnson et al., 1983; Yoder et al., 1988; Adam et al., 2005].

Airway support is required in the majority of cases either via tracheostomy or a tube keeping the nasopharyngeal airway open. This is most commonly required in the first week of life and may be required for several years, or even lifelong. Several patients have had reconstructive surgery incorporating mandibular distraction to improve airway competence, with varying degrees of success. Once no longer dependent on such airway support, many patients have continued to experience airway incompetence, usually presenting as obstructive sleep apnea. This may require airway support into adulthood, either with positive pressure ventilation or nasopharyngeal airway at night. General anesthesia appears safe in experienced hands with several techniques adopted to aid intubation, including ketamine induction, use of a laryngeal mask, and use of a nasopharyngeal airway [Antila et al., 1998; Dernedde et al., 1998; Machotta and Hoeve, 2008].

Hearing

Minor anomalies of external ear morphology and narrow ear canals are common. Many patients have sensorineural or mixed conductive hearing loss in the moderate range. Inner ear malformations have not been noted.

Bone and Connective Tissue

The bone age is invariably reported as advanced at birth and in childhood. Full skeletal surveys however, do not show an advanced bone age elsewhere and only mild abnormal bone maturation in the long tubular bones (wide epiphyses). In the hand, the carpus appears more advanced in age than the phalanges. Therefore it seems more justified to state bone maturation in MSS is abnormal instead of advanced. We consider it as being a dysostosis. Typically the proximal and middle phalanges are wide, bullet shaped or rectangular and terminal phalanges short and narrow (Fig. 3).

MSS has been considered as an example of an overgrowth syndrome. However, stature is typically normal in infancy and

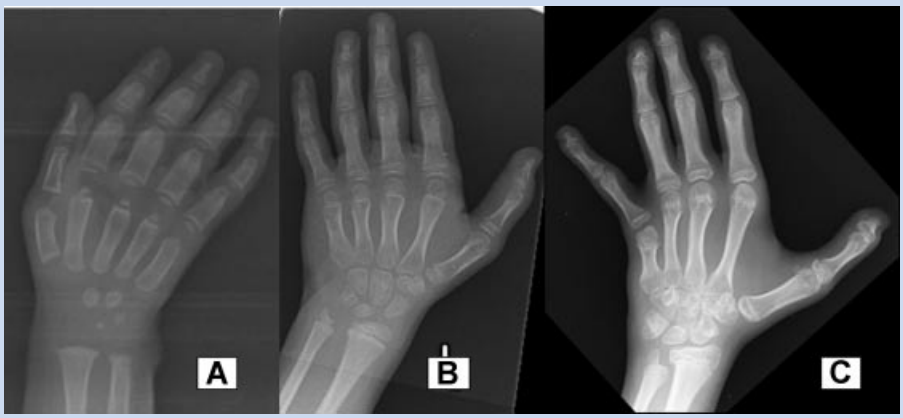

FIG. 3. X-rays of hands at: (A) newborn (Patient 4); (B) 5 years (Patient 8); (C) 12 years (Patient 14).

early childhood, and in the second decade height progressively diverges from normal so that final height is >6 standard deviations below the mean. This is compounded to some degree by (kypho-) scoliosis. There does not appear to be a growth spurt associated with puberty (the timing of which is normal). Thoracic kyphoscoliosis becomes evident in childhood and appears universal by adulthood. No structural abnormalities of the vertebral bodies are usually seen. Surgical rod implants impair already limited growth and mobility, but make lifting and handling easier. Non-traumatic fractures and osteopenia have been reported in some however several patients have sustained significant trauma without fracture, and osteopenia is not universal. Blue-gray sclerae are evident in two thirds of cases, and all patients with non-traumatic fractures had this feature.

Umbilical hernia occurs in around 30% of cases but herniation at other sites are not widely reported. One patient had recurrent herniation after abdominal surgery suggesting a possible defect in connective tissue healing. Scar formation however appears to be normal, and although skin texture is frequently described as soft, there is no evidence of a tendency to bruise easily, and no reports of abnormal bleeding. Joint laxity may be present in the periphery in younger patients, although mild contractures and high muscle tone may also occur. Pes planus appears universal. Gingival hyperplasia is frequent and present in 40%. It may require surgery to maintain oral hygiene. Histology has not been reported so the etiology of this manifestation is unclear.

Abnormalities of the upper cervical spine and skull base have been noted with appearances of hyperostosis, dysplasia, and sclerosis. Radiological evaluation of the cervical spine and skull base with flexion/extension views or other imaging modalities is warranted. Neurological complications are discussed below.

Development and Behavior

Patients show a moderate to severe cognitive deficit, with several behavioral characteristics that were common to many in the cohort. Subjects mostly have a happy demeanor and especially enjoy social interactions with friends and family [van Balkom et al., unpublished work]. A fascination for a favorite toy with which they tend to play in a repetitive, stereotypical manner, appears a common phenomenon. This is often a toy designed to stimulate several senses at once, perhaps appealing to children with impaired hearing and vision. Speech milestones are markedly delayed with many subjects never attaining spoken language, presumably in part due to anomalies of laryngeal and facial anatomy. Motor milestones are also severely delayed with several patients remaining non-ambulant.

Neurology

MSS patients have usually truncal hypotonia and peripheral hypertonia with brisk deep tendon reflexes. This phenotype is present from childhood and appears non-progressive. Drooling of saliva is common and may stem in part from oromotor dysfunction, but is compounded by facial anatomy promoting an open mouth. Two patients developed spastic tetraparesis in infancy secondary to cervical spine compression and another patient had asymptomatic cervical spine stenosis noted on MRI. Neuroradiological imaging has shown a number of structural anomalies such as absent or underdeveloped callosal body; ventriculomegaly; pachygyria; polymicrogyria; and septo-optic dysplasia. Occasional seizures occur but they are not common and no patient is receiving anti-convulsant therapy. We recommend brain imaging in infants presenting with MSS and there should be awareness of the risk of cervicomedullary compression.

Other Findings

Two male patients have developed hypertrophic pyloric stenosis, with a classical presentation at around one month of age. The finding of pyloric stenosis in 2 out of 19 cases may be coincidence, or may be related to other common findings in infants with MSS, such as advanced carpal bone maturation and gingival hypertrophy. One patient of the present cohort developed unilateral Wilms tumor at the age of 4 years. No other patient has been reported with any type of malignancy, but most cases were very young when reported. Further long-term follow-up and cohort studies will be required to

establish whether individuals with MSS have an increased susceptibility to Wilms tumor or other forms of cancer. No screening is currently warranted. Craniosynostosis occurred in one patient and is reported in three from the literature. The affected sutures were the metopic suture in three patients and the posterior segment of the sagittal suture in one. All patients have a thin build with reduced muscle bulk.

Adult Phenotype

The general adult phenotype is characterized by moderate to severe mental retardation, including little or no speech and limited mobility. Adult height and weight are significantly reduced but head circumference is normal. The facial features become more obvious, especially in the proptosis, short nose with anteverted nares, and thick, everted lips. The mouth is often held open showing prominent and irregularly placed teeth and thick gingiva. The tongue may be large and protuberant and drooling is common. Individuals of both sexes are hirsute, particularly on the limbs and back. Adults are cheerful and pleasant in nature, although stubbornness and obsessive traits also occur. Medical problems identified in adulthood are obstructive sleep apnoea, aspiration pneumonia, pulmonary hypertension, and early onset osteoarthritis.

Differential Diagnosis

Much debate can be traced in medical literature whether Marshall–Smith and Weaver syndromes are distinct entities, in part because both syndromes were first described around the same time with advanced skeletal maturation as a principal feature. Careful delineation of the phenotype however, with particular regard to the facial features, radiological findings and natural history, suggests significant differences [Fitch, 1980]. Other syndromes with overlapping phenotypes include Desbuquois chondrodystrophy, Fine–Lubinsky syndrome, pyknodysostosis, Antley–Bixler syndrome, Ehlers-Danlos type VII, galactosyltransferase I deficiency and Lysyl hydroxylase 3 deficiency [Hennekam et al., 2010]. The combination, however, of the distinctive radiological findings, facial dysmorphism, and upper airway pathology, make MSS an easily recognisable and unique entity.

Etiology

All definite cases of MSS have occurred sporadically with, no familial recurrence or parental consanguinity. The gender ratio of reported cases is roughly equal, and there is not an increased prevalence of sub-fertility or miscarriage in the parents of affected individuals. Although one report in the literature described a brother and sister with features suggestive of MSS [Jalaguier et al., 1983], we posit that the clinical features are more suggestive of Weaver syndrome than MSS. One patient with a phenotype suggestive of MSS was found to have an inverted duplication of chromosome 2q [Seidahmed et al., 1999], but other patients with trisomy for this region did not resemble MSS, and no other chromosome abnormalities have been reported. In the present cohort paternal or maternal age at conception was not advanced beyond that of the general population.

The analysis of 12 patient samples by array-CGH did not identify any recurrent pathogenic CNVs within this sample set. These results indicate that at the resolution tested, MSS is not a genomic disorder caused by a recurrent pathogenic CNV.

Marshall–Smith Syndrome Wiki

The term *Wiki* is derived from the Hawaiian phrase for quick, and is used for an online collaborative resource for compiling information from numerous authors. MSS is an extremely rare condition with less than 50 cases reported worldwide, and traditional methods of collating a large series of patients are hampered by geographical distances, underdeveloped healthcare systems in developing countries, and language differences. Compiling anonymous phenotype data on a wiki allowed parents and carers to add comments on aspects of the phenotype or natural history based on their own experiences, thus giving a deeper insight into the natural history of the syndrome and facilitating dialogue between clinicians and families that were spread across 11 countries in Europe and the Americas. This technique also aided recognition of common traits, as sharing experiences allowed families to remember important or significant facts that they had forgotten to report to their clinician. Responses from all families were compiled and used as a basis for re-writing of the final draft of this manuscript. Using the wiki facilitated the development of a much more complete and consistent data-set than would have been possible using retrospective case -note review. It may therefore be a useful adjunct if evaluation of all subjects by a single observer is impractical due to the geographical spread of the patients. Wikis are starting to be used in many areas of science, as a way of more efficiently utilizing collective expertise and sharing information that would otherwise remain hidden in personal files or memories [Hu et al., 2008]. We recommend this technique for future studies attempting to describe the phenotype and natural history of (very) rare diseases.

CONCLUSION

We present a relatively large series of patients with MSS. By including previously reported cases, adults and information obtained from families using a wiki resource, we could further delineate this distinctive and severe multisystem disorder, have gained insight into the natural history of the entity and suggested recommendations for management. Discovery of the molecular cause and evaluation of the long-term physical and medical consequences will further aid medical management, lead to potential treatments and reveal important biological mechanisms in human development and function.

ACKNOWLEDGMENTS

We are very pleased to thank all families for their cooperation during this study, and especially Henk-Willem Laan and Sonja Bracke of the International Marshall–Smith Support group. We thank Isadora Laury, Trine Prescott, Sergio B Sousa, Gwenn Treguier, and Karin Writzl for their help in translating the wiki, Dr. Elham Sadighi-Akha for carrying out the array hybridizations, and Rodger Palmer for additional cytogenetic studies. SJLK and

ES-A are supported by the NIHR Biomedical Research Centre, Oxford and also supported by the Wellcome Trust [075491/Z/04]. A.S. and R.C.M.H. acknowledge a grant from the Marshall–Smith Research Foundation in support of this study.

REFERENCES

Adam MP, Hennekam RC, Keppen LD, Bull MJ, Clericuzio CL, Burke LW, Ormond KE, Hoyme EH. 2005. Marshall–Smith syndrome: Natural history and evidence of an osteochondrodysplasia with connective tissue abnormalities. Am J Med Genet Part A 137A:117–124.

Antila H, Laitio T, Aantaa R, Silvoniemi P, Pakkanen A. 1998. Difficult airway in a patient with Marshall–Smith syndrome. Paediatr Anaesth 8:429–432.

Butler MG. 2004. Marshall–Smith syndrome: Follow-up report of a four and a half year old male. Am J Med Genet Part A 126A:329–330.

Charon A, Gillerot Y, Van Maldergem L, Van Schaftingen MH, de Bont B, Koulischer L. 1990. The Marshall–Smith syndrome. Eur J Pediatr 150:54–55.

Chatel C, Maazoul F, Sigaudy S, Fredouille C, Ayme S, Philip N. 1998. Neonatal death in Marshall–Smith syndrome. Genet Couns 9:15–18.

Cooley SM, O'Connell MP, Keane D. 2004. Marshall Smith syndrome and pregnancy. J Obstet Gynaecol 24:181.

Cullen A, Clarke TA, O'Dwyer TP. 1997. The Marshall–Smith syndrome: A review of the laryngeal complications. Eur J Pediatr 156:463–464.

de la Torre Cecilia MC, Espino AR, Gil Rivas RA, Fernandez GF, Romanos LA. 1989. Marshall–Smith syndrome with clinodactyly, joint instability and retarded language development. An Esp Pediatr 31:148–151.

De Toni E, Duillo MT, de Toni T, Cortese M, Bergamo F. 1976. Unusual syndrome with acceleration of skeletal maturation (Marshall's syndrome). 1st case in the Italian literature. Minerva Pediatr 28:1499–1509.

Dernedde G, Pendeville P, Veyckemans F, Verellen G, Gillerot Y. 1998. Anaesthetic management of a child with Marshall–Smith syndrome. Can J Anaesth 45:660–663.

Deshpande C, Forrest M, Russell-Eggitt I, Hall CM, Mehta R, Paterson J. 2006. Visual impairment and prolonged survival in a girl with Marshall–Smith syndrome. Clin Dysmorphol 15:111–113.

Diab M, Raff M, Gunther DF. 2003. Osseous fragility in Marshall–Smith syndrome. Am J Med Genet Part A 119A:218–222.

Eich GF, Silver MM, Weksberg R, Daneman A, Costa T. 1991. Marshall–Smith syndrome: New radiographic, clinical, and pathologic observations. Radiology 181:183–188.

Endo A, Jin Y, Masunaga K, Shimada M, Fujita Y, Minato M, Takada M, Takahashi S, Harada K. 1995. Marshall–Smith syndrome: Report of a case and review of the literature. Congenital Anomalies 35:285–292.

Ferran JL, Delcor Y, Senac JP, Broche M. 1978. Acceleration of bone maturation in the newborn with facial dysmorphia: Marshall–Smith's syndrome (author's transl). J Radiol Electrol Med Nucl 59:579–583.

Fitch N. 1980. The syndromes of Marshall and Weaver. J Med Genet 17:174–178.

Flatz SD, Natzschka J. 1978. Syndrome of accelerated skeletal maturation, type Marshall (author's transl). Klin Padiatr 190:592–598.

Hassan M, Sutton T, Mage K, Limal JM, Rappaport R. 1976. The syndrome of accelerated bone maturation in the newborn infant with dysmorphism and congenital malformations. (The so-called Marshall–Smith syndrome.) Pediatr Radiol 5:53–57.

Hennekam R, Krantz I, Allanson J. 2010. Gorlin's syndromes of the head and neck. 5th edition. New York: Oxford University Press.

Hu JC, Aramayo R, Bolser D, Conway T, Elsik CG, Gribskov M, Kelder T, Kihara D, Knight TF Jr, Pico AR, Siegele DA, Wanner BL, Welch RD. 2008. The emerging world of wikis. Science 320:1289–1290.

Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, Scherer SW, Lee C. 2004. Detection of large-scale variation in the human genome. Nat Genet 36:949–951.

Iafusco F, D'Avanzo M, Ansanelli V. 1977. A case of accelerated skeletal maturation (Marshall's syndrome). Pediatria (Napoli) 85:487–496.

Jalaguier J, Montoya F, Germain M, Bonnet H. 1983. Acceleration of bone maturation and dysmorphic syndrome in 2 siblings (Marshall–Weaver syndrome). J Genet Hum 31:385–395.

Johnson JP, Carey JC, Glassy FJ, Paglieroni T, Lipson MH. 1983. Marshall–Smith syndrome: Two case reports and a review of pulmonary manifestations. Pediatrics 71:219–223.

Kubota T, Namba N, Nakajima S, Arai H, Ozono K. 2005. A case with Marshall–Smith syndrome without life-threatening complications. Clin Pediatr Endocrinol 14:63–67.

LaPenna R, Folger GM Jr. 1982. Extreme upper airway obstruction with the Marshall syndrome. Clin Pediatr (Phila) 21:507–510.

Machotta A, Hoeve H. 2008. Airway management and fiberoptic tracheal intubation via the laryngeal mask in a child with Marshall–Smith syndrome. Paediatr Anaesth 18:341–342.

Mandim BL, Fonseca NM, Ruzi RA, Temer PC. 2007. Anesthesia in a patient with Marshall–Smith syndrome: Case report. Rev Bras Anestesiol 57:401–405.

Marshall RE, Graham CB, Scott CR, Smith DW. 1971. Syndrome of accelerated skeletal maturation and relative failure to thrive: A newly recognized clinical growth disorder. J Pediatr 78:95–101.

Menguy C, Rival JM, Poisson-Salomon AS, Barbier ML, Fournet JP. 1986. Marshall's syndrome. Apropos of a new case. Ann Pediatr (Paris) 33:339–343.

Moon KO, Shin WJ, Shin YJ, Dong ES, Ahn YM. 2002. A case of Marshall–Smith syndrome. J Korean Pediatr Soc 45:906–911.

Nabrady J, Bozalyi I. 1973. A recent case of accelerated bone development and somato-mental retardation. Orv Hetil 114:2782–2785.

Pappas CT, Rekate HL. 1991. Cervicomedullary junction decompression in a case of Marshall–Smith syndrome. Case report. J Neurosurg 75:317–319.

Perrin JC, Arcinue E, Hoffman WH, Chen H, Reed JO. 1976. Accelerated skeletal maturation syndrome with pulmonary hypertension. Birth Defects Orig Artic Ser 12:209–217.

Roodhooft AM, Van Acker KJ, Van Thienen MN, Martin JJ, Ceuterick C. 1988. Marshall–Smith syndrome: New aspects. Neuropediatrics 19:179–182.

Seidahmed MZ, Rooney DE, Salih MA, Basit OB, Shaheed MM, Abdullah MA, Abomelha A. 1999. Case of partial trisomy 2q3 with clinical manifestations of Marshall–Smith syndrome. Am J Med Genet 85:185–188.

Sharma AK, Haldar A, Phadke S, Agarwal SS. 1994. Marshall–Smith syndrome: A distinct entity. Indian Pediatr 31:1098–1100.

Smyth RL, Gould JD, Baraitser M. 1989. A case of Marshall–Smith or Weaver syndrome. J R Soc Med 82:682–683.

Sperli D, Concolino D, Barbato C, Strisciuglio P, Andria G. 1993. Long survival of a patient with Marshall–Smith syndrome without respiratory complications. J Med Genet 30:877–879.

Sumiya N, Ito Y, Hayakawa O, Oishi Y, Ota M. 2002. Long-term survival of a patient with Marshall–Smith syndrome. Scand J Plast Reconstr Surg Hand Surg 36:114–118.

Summers DA, Cooper HA, Butler MG. 1999. Marshall–Smith syndrome: Case report of a newborn male and review of the literature. Clin Dysmorphol 8:207–210.

Tipton RE, Wilroy RS Jr, Summitt RL. 1973. Accelerated skeletal maturation in infancy syndrome: Report of a third case. J Pediatr 83: 829–832.

Travan L, Oretti C, Zennaro F, Demarini S. 2008. Marshall–Smith syndrome and septo-optic dysplasia: An unreported association. Am J Med Genet Part A 146A:2138–2140.

Visveshwara N, Rudolph N, Dragutsky D. 1974. Syndrome of accelerated skeletal maturation in infancy, peculiar facies, and multiple congenital anomalies. J Pediatr 84:553–556.

Wang TJ. 2002. Marshall–Smith syndrome in a Taiwanese patient with T-cell immunodeficiency. Am J Med Genet 112:107–108.

Watanabe Y, Tanaka Y, Umemura N, Koitabashi T. 2003. A case of Marshall–Smith syndrome. Masui 52:860–862.

Williams DK, Carlton DR, Green SH, Pearman K, Cole TR. 1997. Marshall–Smith syndrome: The expanding phenotype. J Med Genet 34:842–845.

Yoder CC, Wiswell T, Cornish JD, Cunningham BE, Crumbaker DH. 1988. Marshall–Smith syndrome: Further delineation. South Med J 81: 1297–1300.