TABLE II. Summary of Clinical Features in 22 WHS Patients

Patient no.	Age/sex	Minimal deletion sizes in 4p(Mb)	Accompanied duplicated regions	Seizure onset	Status epilepticus	Treatment at the time of this study/course of seizures	CNS complications	Developmental delay
1	6y/F	2.06	dup(10q),772 kb	+/9m	–	CZP/disappeared	–	Moderate (DQ41)/walk at 2y3m
2	13y/F	2.29		+/2y6m	–	VPA/disappeared for 5 years	N.I.	Severe (IQ23)/walk at 7y
3	1y8m/F	2.93	dup(4q),45.6 Mb	+/1y3m	–	–/disappeared after only one attack	–	Severe/no sitting
4	4y3m/F	3.45		+/7m	+	VPA, CLB/occurred frequently	Periventricular leukomalacia	Severe/no head control
5	5y10m/F	5.26		+/1y1m	–	CZP/well-controlled	N.I.	Moderate/walk at 4y
6	16y/F	5.49		+/2y1m	–	DZP/disappeared since 8y	N.I.	Severe/walk at 7y
7	18y/F	6.92		+/6m	+	VPA, Br, Vit B6 (West syndrome)/improved after Br at 1y	–	Severe (IQ10)/walk at 7y
8	6y6m/M	7.51		+/7m	+	TPM, PB, CLB, Br/improved after Br at 3y	N.I.	Severe/roll over at 1y5m
9	5y3m/F	8.09		+/10m	+	PB, VPA/occurred frequently	–	Severe/head control at 12m
10	7m/M	8.77		–	–	–/–	–	Severe
11	8y/F	8.77	dup(8p),6.9 Mb	+/6m	+	VPA, PB/improved after 2y	–	Severe (DQ10)/sit at 4y
12	16y/F	8.77		+/7m	+	VPA, PHT/improved after 2y	Ventricular enlargement	Severe/head control at 2y
13	12y/F	8.85 (1.37–10.22)			–	–/–	–	Moderate/walk at 2y3m
14	5y/F	11.11		+/9m	+	VPA, Br/well-controlled	–	Severe/walk
15	9m/M	12.02		+/8m	+	VPA/continued	Ventricular enlargement	Severe
16	1y11m/F	12.33		+/9m	+	VPA, LGT, CZP/occurred frequently	HCC, Cerebellar atrophy	Severe (DQ30)/head control at 9m
17	18y/F	13.63 (0.84–14.5)		+/1y	+	–/disappeared for several years	HCC	Severe (IQ10)/walk at 5y
18	3y/F	15.70		+/1y2m	+	VPA, CLB, Br/improved gradually	–	Severe/head control
19	2y11m/F	18.60		+/2m	+	PB, CZP, TPM/occurred frequently	–	Severe/no head control
20	4y/F	21.00	dup(11q),1.27 Mb	+/1m	–	VPA, ZNS/disappeared for two years	Cerebral atrophy	Severe/no head control
21	2y10m/F	28.35		+/11m	+	TPM, CLB/disappeared since 2y	Cerebral atrophy	Severe
22	6y/M	29.42		+/2m	+	VPA, ESM, PB/occurred frequently	HCC, Grey matter heterotopia, white matter volume loss	Severe (DQ10)/no head control

Patient no.	Height/weight (SD)[a]	Feeding	CL/CP	Heart	Urogenital	Skeletal	Ophthalmologic	Hearing impairment	Other complication(s)
1	−2.4/−2.0	Oral	−	ASD	−	−	Strabismus	−	
2	−5.4/−3.5	Oral	−	ASD	N.I.	Scoliosis (mild)	−	−	Multiple osteochondromatosis
3	−5.3/−2.3	Tube	−	−	−	−	−	Severe	hypercholesterolemia
4	−4.3/−3.0	Tube	−	ASD, PDA, VSD	N.I.	Limited hip flexion	Strabismus	Moderate	
5	−3.8/−2.9	Oral	−	ASD	N.I.	−	Strabismus	−	Hypercholesterolemia
6	−4.9/−3.0	Oral	−	−	−	N.I.	Strabismus (ET)	−	
7	−5.1/−2.5	Oral	−	PS	Renal hypoplasia, RF	Pes planus	−	Moderate	Hypercholesterolemia, hyperuricemia
8	−6.4/−3.7	Tube	−	−	−	−	NDO	Moderate	Fanconi syndrome due to VPA
9	−5.8/−4.1	Oral	−	ASD, PS	−	−	Strabismus	Moderate	
10	−4.5/−3.9	Tube	+ (CP)	PDA	−	−	Right cataract	−	
11	−4.1/−3.3	Tube	+ (SMCP)	AR	−	N.I.	Strabismus, NDO	−	
12	−11.7/−5.3	Tube	+ (CL/CP)	PS	Renal hypoplasia, RF	Scoliosis (mild)	Strabismus (XT)	Severe	
13	−3.0/−2.3	Tube	−	VSD	−	−	−		
14	−5.2/−4.0	Oral		ASD	−	−	−	Moderate	
15	−2.0/−2.3	Oral	−	ASD, PS	Criptorchidism	−	N.I.	Moderate	
16	−3.4/−2.7	Tube	+ (SMCP)	ASD, PDA	Hydronephrosis	Talipes varus	Strabismus (XT), NDO	−	
17	−5.3/−3.8	Oral	−	ASD	Renal hypoplasia, RF	Acetabular dysplasia	Cataract	−	Hypercholesterolemia
18	−5.6/−4.0	Tube	−	ASD, PS	Renal hypoplasia, RF	Sagittal craniosynostosis	Coloboma	−	Hypercholesterolemia
19	−4.4/−2.4	Tube	−	ASD, PS	−	Scoliosis	Optic nerve atrophy	Moderate	
20	−3.3/−2.6	Tube	−	PDA, VSD	Renal hypoplasia VUR	−	−	Moderate	
21	−2.3/−3.1	GS	+(CP)	ASD, PDA	UJS, RF	Talipes varus Cervical spine abnormalities	−	Severe	
22	−1.3/−1.4	GS	+	ASD	Renal dysplasia, RF, cryptorchidism, hypospadias	−	Cataract, coloboma	Severe	

ASD, atrial septal defect; Br, potassium/sodium bromide; CL, cleft lip; CLB, clobazam; CNS, central nervous system; CP, cleft palate; CZP, clonazepam; DQ, developmental quotient; DZP, diazepam; ESM, ethosuximide; ET, esotropia; F, Female; GS, gastrostomy; HCC, hypoplasia of the corpus callosum; IQ, intelligence quotient; LGT, lamotrigine, M, Male; m, months; NDO, nasolacrimal duct obstruction; N.I., not investigated; PB, phenobarbital; PDA, patent ductus arteriosus; PHT, phenytoin; PS, pulmonary stenosis; RF, renal failure; SMCP, submucous cleft palate; TPM, topiramate; UJS, ureteropelvic junction stenosis; VPA, valproate; VSD, ventricular septal defect; VUR, vesicoureteric reflux; XT, exotropia; y, years; ZNS, zonisamide.

[a]Height and weight were evaluated at the time of this study.

TABLE III. Frequency of Major Structural Defects According to Deletion Sizes

	Small (<6 Mb)	Intermediate (6–15 Mb)	Large (>15 Mb)
Congenital heart defects	4/6 (67%)	10/11 (91%)	5/5 (100%)
Renal abnormalities [renal failure]	0/3 (0%) [0/3]	4/11 (36%) [3/11]	4/5 (80%) [3/5]
Ocular defects	0/6 (0%)	2/11 (18%)	3/5 (60%)
Cleft lip/palate	0/6 (0%)	5/11 (45%)	2/5 (40%)
Skeletal anomalies	2/6 (33%)	4/11 (36%)	3/5 (60%)

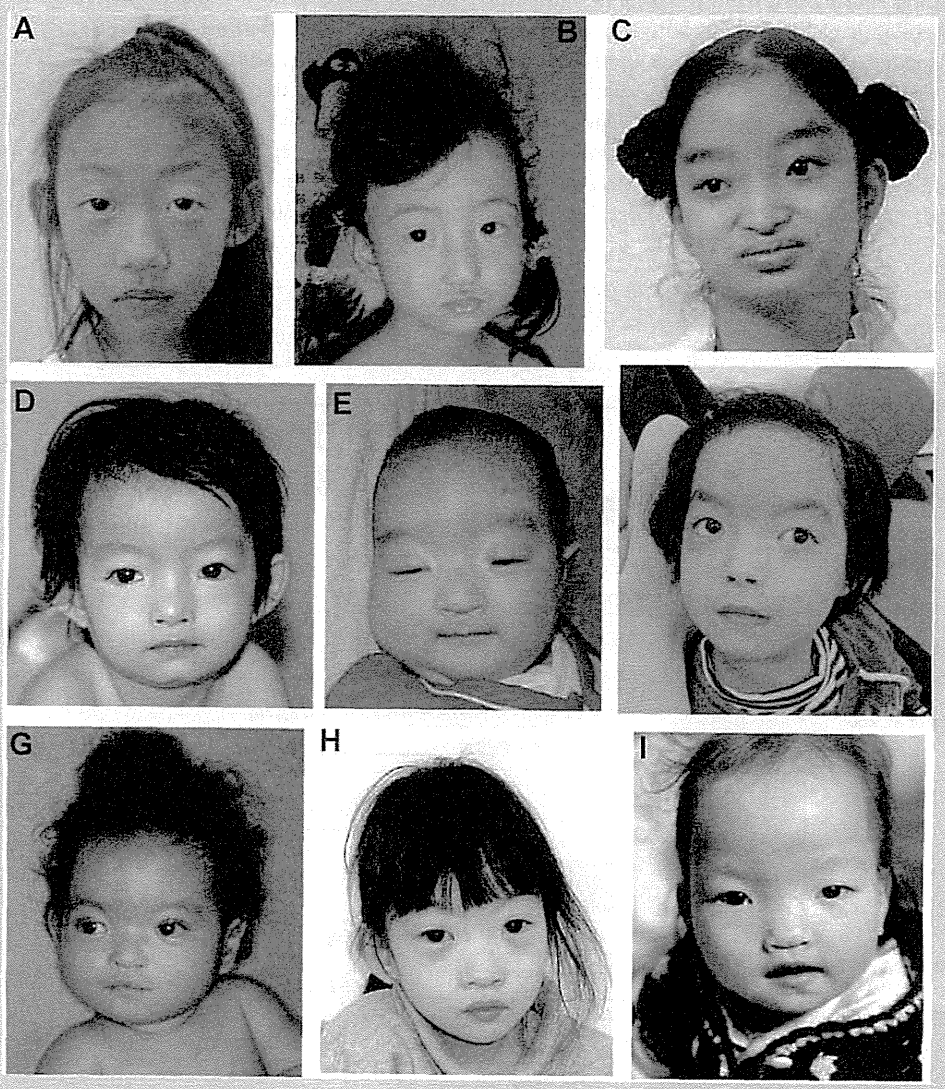

FIG. 4. Clinical photographs. Patient 1 at age 8 years and 10 months (A), Patient 2 at age 4 years (B), Patient 6 at age 18 years (C), Patient 7 at age 2 years and 2 months (D), Patient 8 at age 3 months (E), Patient 11 at age 8 years and 8 months (F), Patient 12 at age 1 year and 3 months (G), Patient 13 at age 6 years and 4 months (H), and Patient 16 at age 2 years and 3 months (I). Typical craniofacial features are present in all the patients except for Patient 1 (A) and Patient 13 (H), showing subtle features without the Greek warrior helmet appearance.

cism between the two patients: 22:8 in Patient 20 and 45:11 in Patient 15.

Our study included four patients with other duplicated chromosomal regions detected by microarray. The duplicated segment of 10q26.3–qter (772 kb) in Patient 1, 11q25–qter (1.27 Mb, mosaicism) in Patient 20, and 8p23.1–pter (6.9 Mb) in Patient 11 have not been reported to associate with extensive disease pathology in a trisomic state [Engelen et al., 2000; Harada et al., 2002; Iwanowski et al., 2011]. The 45.6 Mb duplication at the 4q31.22–qter region in Patient 3 is considered to be mainly associated with psychomotor delay and often with cardiac and renal anomalies [Otsuka et al., 2005; Wang et al., 2009]. Indeed, Patient 3 showed severe developmental delay in spite of a small 4p deletion (2.93 Mb), but no apparent cardiac or renal anomaly.

The severity of seizures is evaluated from the time of onset and the presence of status epilepticus. Six patients with small deletions (<6 Mb) from 4pter tended to have a later onset of seizures and status epilepticus was less common than those patients with intermediate (6–15 Mb) or large deletions (>15 Mb). Developmental delay was severe in most patients, with the exception of three with a moderate delay: two of these had small terminal deletions (2.06 and 5.26 Mb) and one had an intermediate interstitial deletion (8.85 Mb). Seizure severity is, therefore, suggested to correlate with the 4p deletion size, which might result in correlation between severity of developmental delay and the 4p deletion size.

Candidate region(s) for seizures in patients with WHS and possible responsible genes are shown in Figure 5. Although *LETM1* is presently considered to be the major responsible gene for seizures [Endele et al., 1999; Rauch et al., 2001; South et al., 2007], the more distal region of the chromosome has also been suggested as a candidate region for seizure penetrance [South et al., 2008a; Misceo et al., 2012]. Indeed, Patient 13 in our series did not have seizures and had an interstitial deletion (1.37–10.22 Mb from 4pter) encompassing *LETM1* but preserving the distal regions, which is similar to "Case 6" reported by Maas et al. [2008] with an interstitial deletion (1.3–2.5 Mb) including *LETM1* and no seizures. Four patients with seizures were reported to have small distal 4p deletions not including *LETM1* [Faravelli et al., 2007; Maas et al., 2008; Zollino et al., 2008; Misceo et al., 2012]. Considering a patient with ring chromosome 4 and a 4p terminal deletion of 760 kb not experiencing seizures [Concolino et al., 2007], the susceptible gene(s) for seizures in WHS might be localized in the region between 760 kb and 1.3 Mb from the 4pter. In our series, Patient 17 with an interstitial deletion

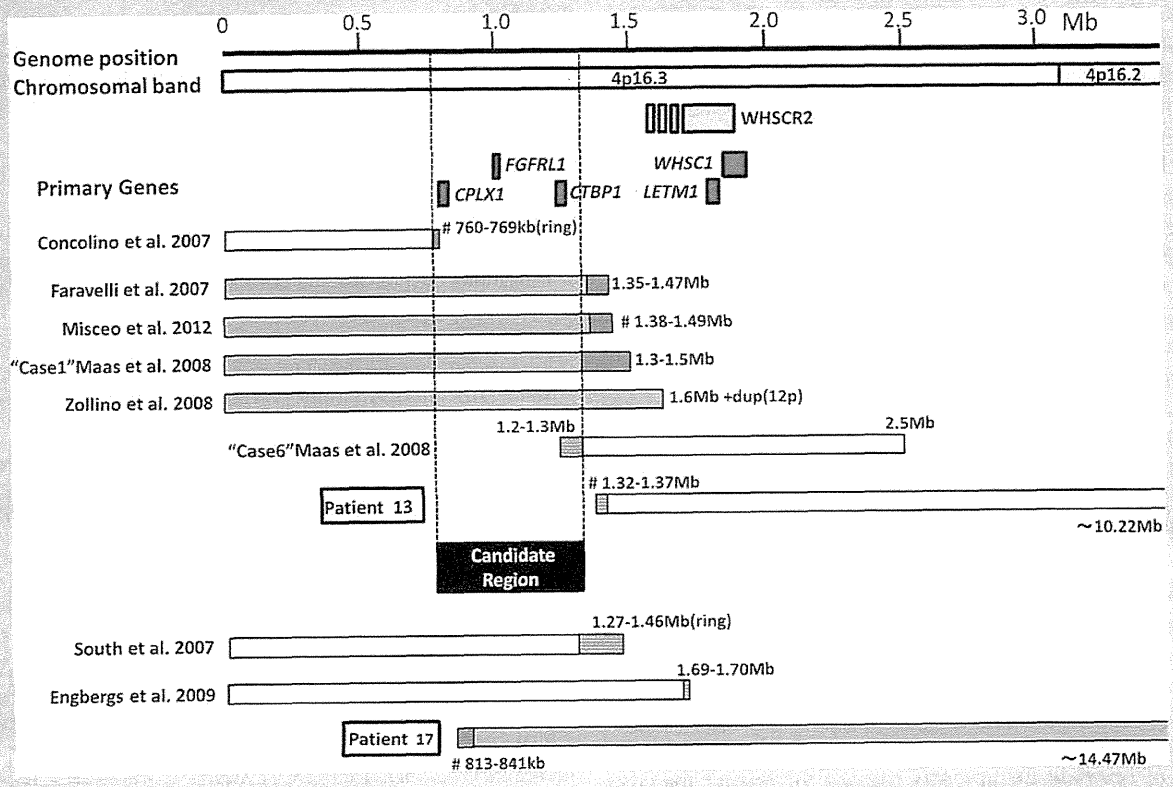

FIG. 5. Schema showing candidate region(s) for the occurrence of seizures [Genome coordinates hg18]. A new candidate region is suggested between 0.76 and 1.3 Mb from 4pter, encompassing *CTBP1* and *CPLX1*, and distal to the previously-supposed candidate gene *LETM1*. White bars indicate deleted segments in patients without seizures. Light gray bars indicate deleted segments in those with seizures. Bars with horizontal stripes indicate deletion breakpoints with variation according to probe-gaps. # Represents patients in whom the breakpoint was determined by oligonucleotide microarray, while breakpoints in the other patients were determined by BAC array or FISH using BAC probes.

encompassing both *LETM1* and most of the new candidate region had severe seizures.

CTBP1 and *CPLX1* are localized in this new susceptible region for seizures. *CTBP1* encodes a transcriptional corepressor that acts at the promoters of many genes [Chinnadurai, 2007]. In an epileptogenic rat model, a ketogenic diet as well as 2-deoxy-D-glucose, a glycolysis-inhibiting drug, reduces epilepsy by stimulating Ctbp activity. Ctbp co-operates with transcriptional factor NRSF to repress expression of BDNF, a strongly suspected epileptogenic signaling molecule [Garriga-Canut et al., 2006]. The hemizygosity of *CTBP1* in WHS patients is therefore considered a potential contributor to the progression of epilepsy [Simon and Bergemann, 2008]. *CPLX1* encodes a type of complexin that binds to syntaxin within the SNARE complex and regulates the fusion of synaptic vesicles [McMahon et al., 1995]. Homozygous *Cplx1* deletion mutant mice develop strong ataxia and sporadic seizures [Reim et al., 2001; Glynn et al., 2005]. These findings suggest that *CTBP1* and *CPLX1* as well as *LETM1* could be susceptibility genes for seizures in WHS.

Bromide therapy was previously reported to be an effective antiepileptic drug in four patients with WHS, in whom it was shown to reduce status epilepticus [Kagitani-Shimono et al., 2005]. In the current study, four patients were administered bromide therapy, which was effective in all. In particular, Patients 7 and 8 showed a marked reduction in seizure frequency after the initiation of bromide therapy. Further information including the types or severity of seizures, electroencephalography (EEG) patterns, efficacy of treatment, and microarray-based deletion mapping in a larger patient series will be necessary to establish a detailed seizure phenotype–genotype correlation.

Hypercholesterolemia, which has not been reported in previous studies, was observed in five patients in the present study, suggesting it to be a noteworthy complication of WHS. *LRPAP1*, localized 3.5 Mb from 4pter, was deleted in four of the patients. *LRPAP1* encodes LDL receptor-related protein-associated protein 1 that plays an important role in lipoprotein metabolism [Willnow et al., 1995], and might therefore be related to hypercholesterolemia. Multifactorial inheritance, including nutritional problems, could also be related to the occurrence of hypercholesterolemia.

In conclusion, this genotype–phenotype correlation study using microarray and FISH-based molecular-cytogenetic investigations uncovered chromosomal rearrangements in all patients including previously unreported complex chromosomal mosaicism. It also demonstrated the correlation of deletion size from 4pter with seizure severity and with occurrence of renal hypoplasia/dysplasia and structural ocular anomalies, and described additional clinical features including hypercholesterolemia. Moreover, a new susceptible region distal to the previously-supposed candidate gene *LETM1* was suggested for the occurrence of seizures, and the usefulness of bromide therapy was stressed for seizure management. To prevent intractable seizures and status epileptics, patients with 4p deletion involving the new susceptible region as well as *LETM1* are recommended to have careful EEG follow-up and intensive pharmacological treatment based on the seizure occurrence and EEG findings, including application of bromide therapy. These findings are relevant to the improvement of WHS healthcare guidelines, as well as to the elucidation of gene(s) function in the deleted region.

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Surgical Intervention for Esophageal Atresia in Patients With Trisomy 18

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Trisomy 18 is a common chromosomal aberration syndrome involving growth impairment, various malformations, poor prognosis, and severe developmental delay in survivors. Although esophageal atresia (EA) with tracheoesophageal fistula (TEF) is a potentially fatal complication that can only be rescued through surgical correction, no reports have addressed the efficacy of surgical intervention for EA in patients with trisomy 18. We reviewed detailed clinical information of 24 patients with trisomy 18 and EA who were admitted to two neonatal intensive care units in Japan and underwent intensive treatment including surgical interventions from 1982 to 2009. Nine patients underwent only palliative surgery, including six who underwent only gastrostomy or both gastrostomy and jejunostomy (Group 1) and three who underwent gastrostomy and TEF division (Group 2). The other 15 patients underwent radical surgery, including 10 who underwent single-stage esophago-esophagostomy with TEF division (Group 3) and five who underwent two-stage operation (gastrostomy followed by esophago-esophagostomy with TEF division) (Group 4). No intraoperative death or anesthetic complications were noted. Enteral feeding was accomplished in 17 patients, three of whom were fed orally. Three patients could be discharged home. The 1-year survival rate was 17%: 27% in those receiving radical surgery (Groups 3 and 4); 0% in those receiving palliative surgery (Groups 1 and 2). Most causes of death were related to cardiac complications. EA is not an absolute poor prognostic factor in patients with trisomy 18 undergoing radical surgery for EA and intensive cardiac management. © 2013 Wiley Periodicals, Inc.

Key words: trisomy 18; esophageal atresia; surgical intervention; neonatal intensive care; survival; causes of death

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INTRODUCTION

Trisomy 18, first described by Edwards et al. [1960], is a common chromosomal aberration syndrome. Patients with the syndrome have prenatal-onset severe growth impairment, characteristic craniofacial features, various visceral and skeletal malformations, and a reduced lifespan; survivors have severe developmental delay [Carey, 2010]. The largest and most cited population-based study

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[Rasmussen et al., 2003] showed a 1-year survival rate of 5–8% and median survival time of 10–14.5 days. The major causes of death were reportedly apnea and withdrawal of treatment, and the presence of a congenital heart defect was not reported to be associated with early death [Embleton et al., 1996; Rasmussen et al., 2003].

Esophageal atresia (EA) with/without tracheoesophageal fistula (TEF) is a common esophageal malformation that occurs in between 1 in 3000–4000 live births. Currently, the best treatment option for EA with TEF in patients with no other severe malformations is primary single-staged correction comprising esophago-esophagostomy and TEF division. For patients with unstable respiratory and/or cardiovascular conditions, however, the procedure should be performed in steps [Pinheiro et al., 2012]. There have been three classification systems of preoperative risks regarding EA: the Waterston classification based on birth weight, associated anomalies, and pneumonia [Waterston et al., 1962]; the Montreal classification based on mechanical ventilation and associated congenital anomalies [Poenaru et al., 1993]; and the Spitz classification based on birth weight and cardiac anomalies [Spitz et al., 1994]. A recent report by Sugio et al. [2006] showed that birth weight might no longer be a risk factor. Patients with EA were reported to have other abnormalities: cardiovascular complications (23%), musculoskeletal malformations (18%), and chromosomal aberrations (5.5%). Patients with life-threatening anomalies, including Potter syndrome, cerebral hypoplasia, and chromosomal abnormalities such as trisomy 13 or 18, as well as infants with totally uncorrectable major cardiac defects or grade IV intraventricular hemorrhage, were recommended to undergo nonoperative management [Pinheiro et al., 2012]. The accurate frequency of EA in trisomy 18 has not been determined by systematic investigation, and only an institution-based study from Japan demonstrated that a total of 33% (8/24) patients with trisomy 18 had EA, representing the most common noncardiac visceral malformation [Kosho et al., 2006]. Although EA with TEF is a potentially fatal complication that can only be rescued through surgical correction, no reports have addressed the efficacy of surgical intervention for EA in patients with trisomy 18.

We herein describe the detailed clinical information of patients with trisomy 18 and EA who were admitted to two Japanese institutions that provided intensive treatment including surgical correction for EA in these patients.

MATERIALS AND METHODS

Patients

Patient data were collected from two institutions in Japan. Nagano Children's Hospital (NCH), established in 1993, is a tertiary hospital for sick children in Nagano Prefecture, which reports roughly 20,000 births per year. Since the obstetric department was established in 2000, pregnant women whose fetuses were found to have severe abnormalities by ultrasonography have also been referred for further evaluation, genetic counseling, and delivery. In the neonatal intensive care unit of this hospital, patients with this syndrome have been managed under the principle of providing intensive treatment based on careful discussion with the parents. The management comprises resuscitation including intratracheal intubation, appropriate respiratory support, establishment of enteral nutrition including corrective and palliative surgery for gastrointestinal malformation, and pharmacological treatment for congenital heart defects. This management was demonstrated to improve survival, with a 1-year survival rate of 25% and median survival time of 152.5 days. The common underlying factors associated with death were congenital heart defects and heart failure (96%) followed by pulmonary hypertension (78%), and the common final modes of death were sudden cardiac or cardiopulmonary arrest (26%) and progressive pulmonary hypertension-related events (26%) [Kosho et al., 2006]. The surgical strategy for EA in patients with trisomy 18 has been to perform gastrostomy soon after birth, followed by a second surgery after stabilization of the general condition (esophago-esophagostomy and TEF division from 1993 to 2003; TEF division from 2003).

The Central Hospital of Aichi Human Service Center (CHAHSC), established in 1970, is a tertiary hospital for sick children and handicapped children/adults covering the northern part of Aichi prefecture and the southern part of Gifu prefecture, which report roughly 70,000 births per year. The management principle of this hospital has been to perform intensive treatment including surgery for every patient, whether he/she has a severe disorder and/or handicap, if he/she needs the treatment or surgery for longer survival and better quality of life. The surgical strategy for EA in patients with trisomy 18 has been to perform esophago-esophagostomy with TEF division as a one-stage operation, whereas a two-stage operation comprising gastrostomy and jejunostomy followed by esophago-esophagostomy was planned in the early period.

A total of 27 patients with karyotypically confirmed full trisomy 18 and EA were admitted to the neonatal intensive care units of NCH from April 1993 to March 2008 and CHAHSC from April 1982 to March 2009. Two patients with A-type EA and one patient who died of uncontrollable respiratory failure before surgery were excluded. The other 24 patients (9 boys, 15 girls; Patients 1, 3, 5, 6, 7, 9, 20–24 from NCH, Patients 2, 4, 8, 10–19 from CHAHSC) with C-type EA who underwent surgery were included in this study (Table I).

Methods

From the medical records of NCH and CHAHSC, we collected detailed clinical data about the surgical methods and courses of EA in the 24 patients including eight who were described in our previous study [Kosho et al., 2006]. In addition, their perinatal conditions and interventions, other medical complications and treatments, and prognosis including survival and discharge were reviewed. We classified the patients into four groups (Table I): Group 1 (Patients 1–6) underwent gastrostomy with/without jejunostomy; Group 2 (Patients 7–9) underwent gastrostomy and TEF division; Group 3 (Patients 10–19) underwent esophago-esophagostomy with TEF division as one operation; and Group 4 (Patients 20–24) underwent gastrostomy followed by esophago-esophagostomy with TEF division.

TABLE I. Clinical Information of Patients With Trisomy 18 Undergoing Surgery for Esophageal Atresia

		Perinatal conditions							Complications				Intervention				Prognosis				
													Surgery for esophageal atresia		Crdiovascular	Respiratory					
Patient	Sex	Gestational age (weeks/days)	Birth weight (g)	Apgar score (1/5 min)	Prenatal diagnosis by amniocentesis	Polyhydramnios	Cesarean section	Resuscitation by intubation	Congenital heart defects	Respiratory complications	Gastrointestinal complications	Urogenital system, Seizure	Methods (age [days] at surgery)	Complications	Cardiac intervention	IMV/extubation (day) or TS	Enteral/oral feeding	Discharge (days)	Survival (days)	Underlying factors associated with death	Final cause of death
Group 1: Gastrostomy+Jejunostomy																					
1	M	31/4	1,017	2/2	−	+	+	+	AVSD, DORV	TA, DE, LH		HU, RD	GS (0)		DO, NG	+/−	−		1	CHD, HF, TA, LH, RsF	RsF
2	M	34/1	1,420		−		−	+	VSD, PDA			HK, IH	GS+JS (1)		D	+/−	+		9	CHD, HF	SCA
3	F	39/3	1,956	2/4	−	+	+	−	ASD, VSD, PDA	RTI			GS (0)	Bleeding	D, DO	+/−	−		12	CHD, PH, HF	Aspiration pneumonia
4	F	35/1	1,464	−/5	−	+	+	+	VSD	PnT	GER	HN	GS+JS (1)		None	+/−	+		20	CHD, PH, Hemorrhagic tendency	PHE, RsF
5	M	36/0	1,220	4/7	−	+	+	+	VSD, PDA		Microileum	HN	GS (0)		D, DG, DO	+/−	−		41	CHD, PH, HF, Malnutrition	HF, PHE
6	M	41/5	1,990	1/5	+	+	−	+	PDA, ASD			Sz	GS (0)		D	+/−	−		133	CHD, PH, HF	HF
Group 2: Gastrostomy+Tracheoesophageal fistula division																					
7	M	34/5	1,515	1/6	−	+	+	+	VSD, PDA				GS (2), TEFD (29)	ChT	D, DG, DO	+/−	+		47	CHD, PH, HF	HF
8	F	35/6	1,152	7/9	+	+	+	−	VSD, ASD, PDA			Sz	GS+TEFD (5)	ChT	D	+/−	+		106	CHD, CLD, PH	HF
9	F	35/2	1,412	5/9	+	+	+	−	AVSD, PDA	Tracheomalacia			GS (0), TEFD (29)		D, NG, PGI2	+/−	+		172	CHD, PH, HF	HF
Group 3: Esophago-esophagostomy+Tracheoesophageal fistula division																					
10	F	37/4	1,776	−/5	−	+	−	+	ASD, VSD, PDA				EES+TEFD (1)		DO	+/−	−		2	CHD, PPHN, HF	SCA
11	F	36/0	1,510	−/5	−		+	+	CoA, VSD, MS, AS			PK, RnF	EES+TEFD (3)		D, PGE1, DO	+/−	+		17	CHD, HF, PK	HF, RnF
12	F	39/4	1,840	5/8	−	+	+	−	VSD, PS	RTI	GER		GS+EES+TEFD (1)		D, DG, DO	+/−	+		17	CHD, RTI, PHE	HF, PHE
13	M	33/5	1,364	8/8	−	+	+	−	ASD, VSD, PDA	RTI		HN, RnF	EES+TEFD (0)		D, DO, PDA ligation	+/−	−		18	CHD, HF	HF, RsF
14	F	41/1	2,320	−/9	−		−	−	VSD, TR			RnF	EES+TEFD (2)		D, DO	+/−	−		23	CHD, PH, HF, RsF	HF
15	M	35/0	938		−	+	−	+	VSD, PH				EES+TEFD (0)		D, DG	+/−	+		27	CHD, PH	SCA
16	F	40/0	1,670	7/8	−	+	+	−	VSD, ASD, PDA	RTI	GER	HK	EES+TEFD (1)		D, DG	+/−	+		70	CHD, PH, RTI	HF
17	M	35/1	1,560	1/4	−	+	−	+	VSD, PDA	RTI	Enteritis Hypertrophic pyloric stenosis		EES+TEFD (2)		D, DO	+/−	+		202	CHD, PH, CLD	HF
18	F	36/0	1,488	5/9	−		+	+	VSD, ASD, PS			Sz	EES+TEFD (1)		D	+/−	+/+		236	CHD, PH	HF
19	F	37/1	1,759	4/7	−	+	+	−	ASD, VSD				EES+TEFD (1)	PnT	D, DG	+/+ (7)	+/+	+ (73)	694	CHD, PH	HF
Group 4: Gastrostomy followed by Esophago-esophagostomy + Tracheoesophageal fistula division																					
20	M	35/4	1,310	7/8	−	+	+	+	VSD, ASD			Sz	GS (0), EES+TEFD (14)	Mediastinitis	D, DO	+/−	+		32	CHD, PH, HF, RsF, Mediastinitis	HF, RsF
21	F	36/4	1,804	1/1	−	+	−	+	VSD, PDA		GER	Sz	GS (1), EES+TEFD (93)	Atelectasis	D, DO, NG	+/+ (125)	+	+ (137)	210	CHD, CLD, PH	SCA
22	M	37/4	1,747	2/3	−	+	+	−	VSD	RTI	AM	HN, Sz	GS (0), EES+TEFD (3)		D, DO, NG	+/TS	+		518	CHD, PH	PH crisis
23	F	36/1	1,422	8/9	−	+	−	−	PDA, VSD (closed)	RTI	GER, AM	Sz	GS (0), EES+TEFD (17)		D	+/−	+		580	RnF, Malnutrition	RnF
24	F	35/1	1,420	5/8	−	+	+	+	PA, VSD, PDA			VUR	GS (1), EES+TEFD (6)	TEF recanalization	D, DG, PGE1	+/TS	+/+	+ (947)	1,786	CHD, PH, HF, RsF	Tube trouble

M, male; F, female; AM, anorectal malformation; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular defect; ChT, chylothorax; CHD, congenital heart defects; CLD, chronic lung disease; CoA, coarctation of aorta; D, diuretics; DE, diaphragmatic eventration; DG, digoxin; DO, dopamine and/or dobutamine; DORV, double outlet right ventricular; EA, esophageal atresia; EES, esophago-esophagostomy; GER, gastroesophageal reflux; GS, gastrostomy; HF, heart failure; HK, horseshoe kidney; HN, hydronephrosis; HU, hydroureter; IH, inguinal hernia; IMV, intermittent mandatory ventilation; JS, jejunostomy; LH, lung hypoplasia; MS, mitral valve stenosis; NG, nitroglycerin; PA, pulmonary atresia; PDA, patent ductus arteriosus; PGE1, prostaglandin E1; PGI2, prostaglandin I2; PH, pulmonary hypertension; PHE, pulmonary hemorrhage; PK, polycystic kidney; PnT, pneumothorax; PPHN, persistent pulmonary hypertension of the newborn; PS, pulmonary stenosis; RD, renal dysplasia; RnF, renal failure; RsF, respiratory failure; RTI, respiratory truct infection; SCA, sudden cardiac or cardiopulmonary arrest; Sz, Seizure; TA, tracheoatresia; TEFD, tracheoesophageal fistura division; TOF, tetralogy of fallot; TR, tricuspid valve regurgitaion; TS, tracheostomy; VSD, ventricular septal defect; VUR, vesicoureteral reflux.

RESULTS

Perinatal Conditions and Interventions

Three patients were prenatally diagnosed with trisomy 18 by amniocentesis. A total of 67% (16/24) of patients were delivered by cesarean, which was selective in six and emergent in eight. Common indications for the cesarean were fetal distress in six, intrauterine growth retardation with polyhydramnios in three, a previous cesarean in one, and breech presentation in one. A total of 58% (14/24) of patients underwent resuscitation by intratracheal intubation. The mean gestational age was 36 weeks and 3 days (range, 31 weeks and 4 days to 41 weeks and 5 days). The mean birth weight was 1,544 g (range, 1,017–1,990 g). The mean Apgar score was 4.0 (range, 1–8) at 1 min and 6.0 (range, 1–9) at 5 min.

Surgery for EA and Surgical Complications

A total of 37% (9/24) of patients (Groups 1 and 2) underwent only palliative surgery. Group 1 (n = 6) underwent only gastrostomy or gastrostomy and jejunostomy on days 0–1. Group 2 (n = 3) underwent gastrostomy on days 0–5 and TEF division on days 5–29.

A total of 63% (15/24) of patients (Groups 3 and 4) underwent radical surgery. Group 3 (n = 10) underwent primary esophago-esophagostomy with TEF division on days 0–3. Group 4 (n = 5) underwent gastrostomy on days 0–1 followed by esophago-esophagostomy with TEF division on days 3–93.

Major surgical complications included hemorrhage (Patient 3), chylothorax (Patients 7 and 8), pneumothorax (Patient 19), mediastinitis (Patient 20), respiratory tract infection and atelectasis (Patient 21), and recanalization of the TEF due to insufficient sutures, requiring reoperation (Patient 24). No intraoperative death or anesthetic complications were noted.

Structural Defects and Medical Complications

All patients had congenital heart defects including ventricular septal defect (VSD), patent ductus arteriosus (PDA), atrial septal defect (ASD), atrioventricular defect, double outlet right ventricle, pulmonary stenosis, coarctation of the aorta, mitral valve stenosis, aortic stenosis, and tricuspid valve regurgitation.

Excluding EA with TEF, noncardiac defects or complications included respiratory abnormalities in 10 patients (42%), such as lung hypoplasia, tracheomalacia, and respiratory tract infection; renal abnormalities in 10 (42%), such as hydroureter, renal dysplasia, horseshoe kidney, polycystic kidney, and renal failure; gastrointestinal abnormalities in 10 (42%), such as gastroesophageal reflux, hypertrophic pyloric stenosis, and anorectal malformation; and seizures in 8 (33%).

Patients 22 and 24 underwent tracheostomy for persistent respiratory failure for the purpose of discharge. Patient 18 underwent Ramstedt procedure for hypertrophic pyloric stenosis. Patient 22 underwent colostomy for anorectal malformation.

Treatment and Courses of Cardiac Defects

A total of 96% (23/24) of patients received cardiovascular drugs. Diuretics (furosemide with/without spironolactone) and dopamine with/without dobutamine pressors were commonly used for heart failure. Prostaglandin E1 was administered to two patients with PDA-dependent congenital heart defects. Nitroglycerin was given to four patients with severe persistent pulmonary hypertension of the newborn. Patient 13 underwent PDA ligation. Patient 8 underwent pulmonary artery banding for a large left-to-right shunt by ASD, VSD, and PDA, but the banding had to be released during the same operation because of worsening of pulmonary hypertension.

Enteral Feeding

A total of 71% (17/24) of patients underwent enteral feeding: 33% in Group 1, 100% in Group 2, 70% in Group 3, and 100% in Group 4. A total of 12.5% (3/24) of patients underwent oral feeding: 20% in Group 3 and 20% in Group 4.

Prognosis

A total of 12.5% (3/24) of patients were discharged home. All the patients had died at the time of this study. Survival rates at 1 day, 1 week, 1 month, and 1 year of age were 100%, 92%, 58%, and 17%, respectively. The overall median survival time was 44 days (range, 1–1,786 days): 88 days in girls and 36.5 days in boys. The median survival time in Groups 1, 2, 3, and 4 was 16 days (range, 1–133 days), 106 days (range, 47–172 days), 25 days, (range, 2–694 days), and 518 days (range, 32–1786 days), respectively. A survival curve for each group is shown in Figure 1A.

Cause of Death

Cause of death was classified into underlying factors associated with death and final mode of death, as described by Kosho et al. [2006] and Kaneko et al. [2008]. The most frequent underlying factors associated with death were congenital heart defects and heart failure in 23 patients (96%), followed by pulmonary hypertension in 18 patients (78%). The most frequent final mode of death was heart failure in 14 patients (58%), followed by respiratory failure and/or pulmonary hemorrhage in five (20%) and sudden cardiac or cardiopulmonary arrest in four (17%).

DISCUSSION

This is the first series to describe the efficacy of surgical intervention for EA with TEF in patients with trisomy 18. Even the natural history of these patients has not been elucidated. A recent support group-based study from Japan [Kosho et al., 2013] described nine patients with EA, with the rate of being offered intensive treatment as 29% (2/7), that of receiving IMV as 57% (4/7), and that of undergoing surgery as 22% (2/9). Survival rate at age 1 year was 0%, and the median survival time was 15.5 days (range, 0–88 days) and was 4 days (range, 0–32 days) without surgical intervention. Statistical analysis showed the presence of EA to be a significant factor associated with shorter survival (<1 year). Our current study shows the survival rate at age 1 year to be 17% and the median survival time to be 44 days. It is, therefore, no doubt that surgical intervention, probably coupled with intensive neonatal treatment,