total of analyzed DMRs [7–9]. Notably, the co-existing methylation abnormalities were predominantly observed as mild hypermethylations of maternally methylated DMRs and were restricted to a single DMR or two DMRs in patients with multilocus abnormalities. Such findings are obviously inexplicable not only by assuming a *ZFP57* mutation that is known to cause severely abnormal methylation patterns of multiple DMRs or a *ZAC1* mutation that may affect methylation patterns of multiple DMRs [37–39], but also by assuming defective maintenance of methylation in the postzygotic period [7]. Thus, some factor(s) susceptible to the co-occurrence of hypomethylation of the *H19*-DMR and hypermethylation of other DMR(s) might be operating during a gametogenic or postzygotic period in cases with *H19*-DMR epimutation.

The patients with multilocus methylation abnormalities had no specific clinical features other than SRS-compatible phenotype. Previous studies have also indicated grossly similar SRS-like phenotype between patients with monolocus and multilocus hypomethylations [7], although patients with multilocus hypomethylation occasionally have apparently severe clinical phenotype [7]. These findings would argue for the notion that the *H19*-DMR epimutation has an (epi)dominant clinical effect. Indeed, *H19*-DMR hypomethylation has led to SRS-like phenotype in a patient with parthenogenetic chimerism/mosaicism [21], whereas *H19*-DMR hypermethylation has resulted in Beckwith-Wiedemann syndrome-like phenotype in patients with androgenetic mosaicism [40].

An extremely hypomethylated *ARHI*-DMR was found in case 13. In this regard, it is known that *ARHI* with a potentially cell growth suppressor function is normally expressed from paternally inherited chromosome with unmethylated *ARHI*-DMR [41]. Indeed, hypermethylation of the *ARHI*-DMR, which is predicted to result in reduced expression of *ARHI*, has been identified as a tumorigenic factor for several cancers with an enhanced cell growth function [42,43]. Thus, it is possible that hypomethylation of the *ARHI*-DMR has led to overexpression of *ARHI*, contributing to the development of typical SRS phenotype in the presence of a low but relatively preserved MI of the *H19*-DMR in case 13.

Oligonucleotide array CGH identified a ~3.86 Mb deletion at chromosome 17q24 in case 73 of group 3. This provides further support for the presence of rare copy number variants in several SRS patients and the relevance of non-imprinted gene(s) to the development of SRS [10]. Interestingly, the microdeletion overlap with that identified in a patient with Carney complex and SRS-like features [44], and the overlapping region encompasses a ~65 kb segment defining the breakpoint of a *de novo* reciprocal translocation involving 17q23–q24 in a patient with SRS-like phenotype (Figure 4) [45,46]. Furthermore, the translocation breakage has affected *KPNA2* involved in the nuclear transport of proteins [46–48]. Thus, *KPNA2* has been regarded as a candidate gene for SRS, although mutation analysis of *KPNA2* has failed to detect a disease-causing mutation in SRS patients [49].

Lastly, it would be worth discussing on the comparison between pyrosequencing analysis and COBRA. Since the same 43 patients were found to have low MIs by both analyses, this implies that both methods can be utilized as a diagnostic tool. While the distribution of the MIs was somewhat different between the two methods, this would primarily be due to the difference in the employed methods such as the hybridization efficiency of utilized primers. Importantly, pyrosequencing analysis was capable of studying plural CpG dinucleotides at the CTCF6 binding site, whereas COBRA examined only single CpG dinucleotides outside the CTCF6 binding site. Thus, the MIs obtained by pyrosequencing analysis would be more accurate than those obtained by COBRA in terms of *IGF2* expression levels, and this would underlie the reasonable correlations of MIs yielded by pyrosequencing analysis with body and placental growth parameters.

In summary, the present study provides useful information for the definition of molecular and clinical findings in SRS. However, several matters still remain to be elucidated, including underlying mechanisms in SRS patients with no *H19*-DMR epimutation or upd(7)mat and the DMR(s) and imprinted gene(s) responsible for the development of SRS in patients with upd(7)mat. Furthermore, while advanced maternal age at childbirth has been shown to be a predisposing factor for the development of upd(15)mat because of increased non-disjunction at meiosis 1 [50], such studies remain fragmentary for upd(7)mat, primarily because of the relative paucity of upd(7)mat. Further studies will permit a better characterization of SRS.

Supporting Information

Figure S1 Methylation analysis of the KvDMR1 using COBRA. A. Schematic representation of the KvDMR1. A 326 bp region harboring 24 CpG dinucleotides was studied. The cytosine residues at the CpG dinucleotides are usually methylated after paternal transmission (filled circles) and unmethylated after maternal transmission (open circles); after bisulfite treatment, this region is digested with *Hpy*188I when the cytosine at the 5th CpG dinucleotide (indicated with a green rectangle) is methylated and with *Eci*I when the cytosines at the 22nd CpG dinucleotide (indicated with a pink rectangle) is methylated. *KCNQ1OT1* is a paternally expressed gene, and *KCNQ1* and *CDKN1C* are maternally expressed genes. B. Representative COBRA results. U: unmethylated clone specific bands; M: methylated clone specific bands; and BWS: Beckwith-Wiedemann syndrome patient with upd(11p15)pat. C. Histograms showing the distribution of the MIs (the horizontal axis: the methylation index; and the vertical axis: the patient number).
(TIF)

Table S1 Primers utilized in the methylation analysis and microsatellite analysis.
(XLS)

Table S2 The results of microsatellite analysis.
(XLSX)

Table S3 Methylation indices for multiple differetially methylated resions (DMRs) obtained by COBRA in 38 patients with Silver-Russell syndrome.
(XLSX)

Table S4 Clinical findings in two unique patients.
(DOC)

Table S5 Correlation analyses in patients with H19-DMR hypomethylations.
(DOC)

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Author Contributions

Conceived and designed the experiments: TF KY TO. Performed the experiments: TF KN CT S. Sano K. Matsubara MK KY. Analyzed the data: TF KN KH KY. Contributed reagents/materials/analysis tools: SM TN TH RH YM K. Muroya TK CN S. Sato TO. Wrote the paper: TO.

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RESEARCH ARTICLE

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Surgical Intervention for Esophageal Atresia in Patients With Trisomy 18

Eriko Nishi,[1,2] Shigeru Takamizawa,[3] Kenji Iio,[4] Yasumasa Yamada,[5] Katsumi Yoshizawa,[3] Tomoko Hatata,[3] Takehiko Hiroma,[6] Seiji Mizuno,[7] Hiroshi Kawame,[8] Yoshimitsu Fukushima,[2] Tomohiko Nakamura,[6] and Tomoki Kosho[1,2]*

[1]Division of Medical Genetics, Nagano Children's Hospital, Azumino, Japan

[2]Department of Medical Genetics, Shinshu University Graduate School of Medicine, Matsumoto, Japan

[3]Department of Surgery, Nagano Children's Hospital, Azumino, Japan

[4]Department of Surgery, Central Hospital, Aichi Human Service Center, Kasugai, Japan

[5]Department of Neonatology, Central Hospital, Aichi Human Service Center, Kasugai, Japan

[6]Division of Neonatology, Nagano Children's Hospital, Azumino, Japan

[7]Department of Pediatrics, Central Hospital, Aichi Human Service Center, Kasugai, Japan

[8]Department of Genetic Counseling, Graduate School of Humanities and Sciences, Ochanomizu University, Tokyo, Japan

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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.

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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*Correspondence to:
Tomoki Kosho, Department of Medical Genetics, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan.
E-mail: ktomoki@shinshu-u.ac.jp
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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 non-cardiac 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,

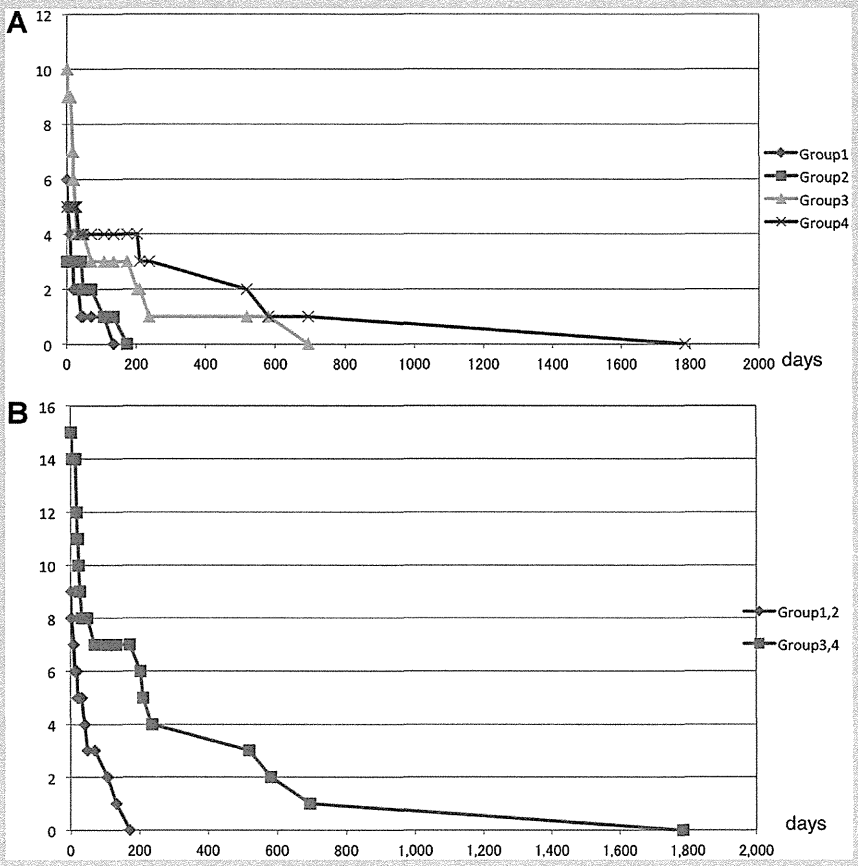

FIG. 1. Survival curves. A vertical axis shows numbers of survivors. A transverse axis shows days after birth. A: Survival curves for Group 1, 2, 3, and 4. B: Survival curves for Groups 1 and 2 (palliative surgery group) and Groups 3 and 4 (radical surgery group).

would contribute to longer survival in patients with trisomy 18 and EA.

The data in the current study were obtained from two children's hospitals in Japan, where surgeons and neonatologists proposed the most effective treatment (surgical procedure, respiratory support, mainly pharmacological cardiovascular support, and other neonatal intensive care) that they considered when they saw each patient, for the purpose of establishment of enteral feeding, discharge, and longer survival. All the parents consented the proposals and no patients had withdrawal care or comfort care in this study period. NCH proposed a two-stage operation with the first procedure as gastrostomy and the second as esophago-esophagostomy with TEF division from 1993 to 2003 and only TEF division from 2003. CHAHSC proposed a two-stage operation with gastrostomy and jejunostomy followed by esophago-esophagostomy with TEF division in the early period and then a one-stage operation with gastrostomy and esophago-esophagostomy with TEF division. As a result, intervention for EA was retrospectively classified into four types (Group 1–4). Thus, the classification would reflect not only the severities of non-EA complications including congenital heart defects accompanied by heart failure and pulmonary hypertension but also surgical strategy for each patient depending on the hospital and the period, irrespective of severity of non-EA complications.

Patients included in each group are characterized as follows. There were only two patients (Patients 1 and 10) who could indeed be judged as "lethal." They could not survive past the first operation because of uncontrollable respiratory failure due to pulmonary hypoplasia in Patient 1, and sudden cardiac arrest due to primary pulmonary hypertension in Patient 10. *Group 1*: Patients in Group 1 only had the first palliative operation (gastrostomy with/without jejunostomy), and died before the second radical operation because of progressive heart failure and/or pulmonary hypertension due to large left-to-right shunts. *Group 2*: Two patients in Group 2, both in NCH from 2003, underwent gastrostomy and TEF division in two stages according to the institutional strategy. Patient 8 from CHAHSC underwent gastrostomy and TEF division in one stage because esophago-esophagostomy was not available due to the long gap between the upper and lower esophagus. All three patients died of progressive heart failure and/or pulmonary hypertension due to large left-to-right shunts. *Group 3*: Nine patients in Group 3 survived past the one-stage radical operation of esophago-esoph-

agostomy with TEF division. Five of them died within 30 days after the operation (progressive heart failure and/or pulmonary hypertension due to large left-to-right shunts in four and heart failure and renal failure due to coarctation of the aorta in one). The other four patients who survived past the neonatal period finally died of progressive heart failure and/or pulmonary hypertension due to large left-to-right shunts. Thus, the differences between the five non-survivors and the four survivors might be related mainly to their cardiovascular conditions, namely, differences in the severities of original cardiac lesions in view of developing heart failure and pulmonary hypertension and/or differences in intra- and post-operative cardiac management. *Group 4:* Three patients in Group 4 survived past 1 year, and two could be discharged home. Deaths of the four patients in Group 4 were associated with cardiac problems. Patient 20 might have survived longer if his postoperative course had not been complicated by mediastinitis.

Patients in Group 4 showed the longest survival with the median survival time as 518 days (range, 32–1786 days), followed by those in Group 2 with the median survival time as 106 days (range, 47–172 days), those in Group 3 with the median survival time as 25 days (range, 2–694 days), and those in Group 1 with the median survival time as 16 days (range, 1–133 days). We compare those who had radical surgery (Groups 3 and 4) with those who didn't (Groups 1 and 2). Survival rate at age 1 year was 27% (4/15) in Groups 3 and 4 and 0% (0/9) in Groups 1 and 2, and the median survival time was 56 days in Groups 3 and 4 and 31 days in Groups 1 and 2 (Fig. 1B). Most importantly, patients with trisomy 18 and EA could not survive long without radical surgery for EA. Factors in prognostic difference between patients in Group 3 (one-stage operation) and those in Group 4 (two-stage operation) is discussed as follows: firstly, patients in Group 3 might have severer non-EA complications, especially congenital heart defects accompanied by heart failure and pulmonary hypertension. However, no apparent difference of non-EA complications was noted (Table I), except Patient 10 who had fatal pulmonary hypertension leading to sudden death on the next day of radical surgery. Secondly, a one-stage operation on the 0–3 days after birth might be too invasive for potentially unstable cardiopulmonary status, especially persistent pulmonary hypertension, in any patients with trisomy 18 complicated by typical left-to-right shunts. The inter-operative period between the first gastrostomy and the second esophago-esophagostomy with TEF division might have been meaningful in careful assessment of patients' physical conditions (reduction of pulmonary hypertension could be expected) and appropriate treatment for patients with unstable cardiopulmonary conditions.

Management of neonates with trisomy 18 has long been discussed from an ethical point of view. Traditional ways of managing patients with this syndrome had been a noninterventional approach, meaning avoidance of emergency surgery [Bos et al., 1992; Paris et al., 1992], labeling this condition as "lethal" or these patients as "hopeless" beings. For the last two decades, however, trends in neonatal intensive care have resulted in the attachment of greater importance to parental decision-making, seeking the "best interest of the child" [Carey, 2010]. Currently, a balanced approach is recommended when counseling families of neonates with this syndrome, comprising the presentation of accurate figures for survival; avoidance of language that assumes outcome such as "lethal," "hopeless," or "incompatible with life"; accurate communication of developmental outcomes that does not presuppose a family's perception of quality of life; and recognition of the family's choice, whether it be comfort care or interventions [Carey, 2012]. In Japan, trisomy 18 had been classified, together with trisomy 13, into a condition in which no additional treatments were considered, but ongoing life-supporting procedures or routine care (temperature control, enteral nutrition, skin care, and love) were not withdrawn [Nishida et al., 1987]. This categorization had a considerable influence on the field of neonatology in Japan, but no legal or social obligation. Thus, babies with trisomy 18 have actually been managed according to an individual policy at each hospital [Kosho, 2008]. The categorization had a harmful effect on physicians in terms of inflexible and paternalistic attitudes toward parents of neonates with severe disorders/disabilities, especially trisomy 18 and trisomy 13. Thus, in 2004, a research project founded by the Ministry of Health, Labour and Welfare, Japan proposed guidelines entitled "Guidelines for Healthcare Providers and Parents to Follow in Determining the Medical Care," which presented a general principle of coping with families of neonates with severe disorders/disabilities, stressing the importance of frank discussion and equal communication between medical staff members and families to seek the "best interests of the babies" [Kosho, 2008]. An increasing number of hospitals have followed the guideline, and important evidences about specific intensive treatments for patients with trisomy 18 have been published recently from single or multiple institutions in Japan: cardiac surgery [Kaneko et al., 2008, 2009; Kobayashi et al., 2010; Maeda et al., 2011] and treatment of seizures [Kumada et al., 2010, 2013]. A recent support group-based study from Japan showed that children with trisomy 18 could live longer and be discharged home through standard intensive treatment such as cesarean and respiratory support, achieve slow but constant psychomotor maturation if they survive, and interact with their families; and that the parents could adapt well [Kosho et al., 2013]. Positive parental feelings have also been demonstrated in several studies from US [Walker et al., 2008; Bruns, 2010; Janvier et al., 2012]. Based on these findings, an intensive approach in the care of children with trisomy 18, adjusted to individual physical conditions and considering parental feelings, can be justified [Kosho et al., 2013]. Two-stage operation would be preferable in management of EA in patients with trisomy 18 in that the inter-operative period could be spent for frank discussion with the parents in view of considerable informed consent seeking "the best interest of the child".

This study has several limitations. First, the number of patients included is small. Second, patient grouping/classification according to the intervention-type is retrospective, not prospective with appropriate randomization as discussed above. Third, the period during which the patients included in this study spans over 20 years. During these years, there could have been considerable changes in the systems or management of the neonatal intensive care units or in the surgical techniques or devices. These limitations are inevitable in discussing management of rare diseases, but could be critical for meaningful generalization. For the readers to interpret the data fairly, we present the detailed clinical background of each patient in Table I. Also, we thoroughly describe how patients received each

intervention for EA and carefully discuss relationship between intervention and prognosis.

In conclusion, EA with TEF would not be an absolute poor prognostic factor in patients with trisomy 18 under a medical environment where radical surgery including esophago-esophagostomy and TEF division and concurrent intensive cardiac management are available. Such an intensive approach could be justified based on increasing evidences about efficacy of intensive treatment, slow but constant development in survivors, and positive parental feelings. Currently, the authors propose a two-stage operation (gastrostomy followed by esophago-esophagostomy and TEF division) in that the inter-operative period could be meaningful in careful assessment of patients' physical conditions, appropriate treatment for patients with unstable cardiopulmonary conditions, and frank discussion with the parents in view of considerable informed consent seeking "the best interest of the child." This information is crucial when counseling parents whose child is prenatally or postnatally diagnosed with trisomy 18 with EA and who are considering the options regarding intensive treatment of their child.

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