RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Natural History and Parental Experience of Children With Trisomy 18 Based on a Questionnaire Given to a Japanese Trisomy 18 Parental Support Group

Tomoki Kosho,[1]* Hideo Kuniba,[2] Yuko Tanikawa,[3] Yoko Hashimoto,[4] and Hiroko Sakurai[5,6]

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

[2]Department of Pediatrics, Nagasaki University School of Medicine, Nagasaki, Japan

[3]Department of Nursing, Kobe City College of Nursing, Kobe, Japan

[4]Sanno Institute of Psychology, Tokyo, Japan

[5]Trisomy 18 Support Group in Japan, Kyoto, Japan

[6]Graduate School of Core Ethics and Frontier Sciences, Ritsumeikan University, Kyoto, Japan

Manuscript Received: 13 February 2012; Manuscript Accepted: 19 March 2013

We conducted a questionnaire-based study in collaboration with a Japanese trisomy 18 parental support group. Sixty-five children (female, 68%) with full trisomy 18 were evaluated. Diagnosis was made prenatally in 17% (11/65) and 57% (37/65) were born following a cesarean. The mean gestational age at delivery was 38 weeks and 6 days, and the mean birth weight was 1,920 g (−2.6SD). A total of 51% (24/47) of children had apneic episodes. Thirteen children experienced generalized seizures, and a minority was seizure-free with medication. Parents of 36% (18/50) of children were offered intensive treatment. A total of 45% (27/60) of children received intermittent mandatory ventilation, which was weaned off in half of them. Nine had surgeries, including esophageal atresia/omphalocele correction, cardiac surgery, and tracheostomy. A total of 15% (8/55) were fed fully orally, and 45% (29/64) were discharged home. Slow but constant psychomotor development was observed, and in four long-term survivors over 10 years, two walked unassisted. Factors significantly associated with survival over 1 year included diagnosis after birth, absence of prematurity, heavier birth weight, absence of esophageal atresia, extubation, ability to feed orally without medical assistance, and home discharge. Parents appeared to be positive about caring for their children, and the children seemed to interact with parents and siblings as long as they lived, resulting in quality family time. The family point of view, as well as knowledge of natural history, should be considered when policy statements about the care of children with trisomy 18 are made.

Key words: trisomy 18; management; support group; questionnaire; natural history; parental experience

How to Cite this Article:
Kosho T, Kuniba H, Tanikawa Y, Hashimoto Y, Sakurai H. 2013. Natural history and parental experience of children with trisomy 18 based on a questionnaire given to a Japanese trisomy 18 parental support group.
Am J Med Genet Part A.

INTRODUCTION

Trisomy 18 is the third most common autosomal aberration syndrome in liveborn infants after trisomy 21 and 22q11.2 deletion syndrome, with an estimated prevalence of 1 in 3,600 to 1 in 8,500, and a 3:1 female to male ratio [Jones, 2006; Carey, 2010]. Children with this syndrome typically manifest prenatal-onset growth impairment, profound psychomotor disability, complications in cardiovascular, respiratory, gastrointestinal, genitourinary, skeletal, sensory, and visual systems, and tumor susceptibility [Jones, 2006; Carey, 2010]. Population-based studies have shown that the 1-year survival of trisomy 18 is 0–10%, the median survival time is 3–14.5 days, and the most common cause of death is not a cardiac lesion but apnea [Carter et al., 1985; Young et al., 1986; Goldstein and

Conflict of interest: none.
Grant sponsor: The Ministry of Education, Culture, Sports, Science and Technology of Japan; Grant numbers: #16790607; #18790758; Grant sponsor: Japanese Ministry of Health, Labour and Welfare.
*Correspondence to:
Tomoki Kosho, M.D., 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
Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2013
DOI 10.1002/ajmg.a.35990

Nielsen, 1988; Root and Carey, 1994; Embleton et al., 1996; Naguib et al., 1999; Nembhard et al., 2001; Brewer et al., 2002; Rasmussen et al., 2003; Niedrist et al., 2006; Vendola et al., 2010].

Management of children with trisomy 18 is controversial. Traditionally, perinatal management of children with this syndrome involved a noninterventional approach [Carey, 2010], including avoidance of delivery by a cesarean [Schneider et al., 1981; Rochelson et al., 1986] and withholding of surgery [Bos et al., 1992], an approach based on the labeling of these children as "lethal" or "hopeless". Early versions of *Smith's Recognizable Patterns of Human Malformation (~4th editions)* state: "Once the diagnosis has been established, the author recommends limitation of all medical means for prolongation of life" [Jones, 1988]. The trend in neonatal intensive care in the last two decades has attached greater importance to parental decision-making, seeking the "best interest of the child" [Carey, 2010]. More recent versions of *Smith's Recognizable Patterns of Human Malformation (5–6th editions)* state: "Once the diagnosis has been established, limitation of extraordinary medical means for prolongation of life should be seriously considered. However, the personal feelings of the parents and the individual circumstances of each infant must be taken into consideration" [Jones, 2006]. However, recent neonatal resuscitation guidelines in 2010 from the American Heart Association [Kattwinkel et al., 2010] and European Resuscitation Council [Nolan et al., 2010] state that the syndrome is included in the conditions in which clinicians should not hesitate to withdraw support because functional survival is highly unlikely.

In many countries, children with trisomy 18 have pure palliative or end-of-life care, based on the notion that the syndrome is a "lethal" condition that is incompatible with life [Merritt et al., 2012]. However, the situation is different in Japan. Although trisomy 18 was categorized as a condition in which no additional treatments were considered but ongoing life-supporting procedures or routine care were not withdrawn [Nishida et al., 1987], children with this syndrome have actually been managed according to an individual policy at each hospital [Kosho, 2008]. A considerable number of hospitals have provided intensive treatment, including standard neonatal intensive care with/without cardiac surgery, based on careful and frank discussion with the parents, and a significantly longer survival has been observed under such intensive approaches [Kosho et al., 2006; Kaneko et al., 2008, 2009; Matsumoto et al., 2008; Maeda et al., 2010].

There is a serious gap between what healthcare providers think about trisomy 18 and what the parents think about their children. Almost all of the parents of children with trisomy 13 or 18 have described that their child was a happy child and enriched their life despite his/her severe disabilities, whereas most of the parents were told by some healthcare providers that their child was incompatible with life [Janvier et al., 2012]. Some parents have lost their children with trisomy 18 because of the one-sided paternalistic approach of healthcare providers with no sincere discussion based on what the parents wanted in terms of the best interests of their children [Farlow, 2008; Thiele, 2010].

To establish better management of children with trisomy 18 and more satisfactory counseling to the parents, further delineation of the natural history of trisomy 18 is crucial. This includes intervention and its efficacy, and parental experience-based evidence on how the child lives his/her life and how the parents think about their child.

Therefore, we performed a questionnaire-based comprehensive study in collaboration with a Japanese trisomy 18 support group, the "Trisomy 18 Support Group in Japan" (http://18trisomy.com/). We collected detailed clinical information of the children and parental experiences, which are expected to contribute to comprehensive characterization of children with trisomy 18. These data could have the potential to disprove the stigma that children with this syndrome consistently die in early infancy and are non-functioning and to establish a new view that they potentially survive for at least several months with an appropriate individualized intensive treatment and interact with others as long as they live.

MATERIALS AND METHODS

Questionnaires were sent by mail to 125 families (one questionnaire for each child but not for each parent) who belonged to the Trisomy 18 Support Group in Japan in October, 2003. The group, established in 2001, now consists of over 340 families who have or had children or fetuses with trisomy 18, with approximately 30 professionals. The questionnaires included 105 questions regarding medical issues (pregnancy, delivery, resuscitation, structural defects, complications, medical treatment, surgery, immunization, early intervention, growth, development, survival, and cause of death), daily lives, welfare, and parental experience with their children with trisomy 18. The study was originally planned as an official project of the group, represented by the president (HS). Professional members of the group (TK, HK, pediatrician/clinical geneticist; YT, nurse/midwife; and YH, clinical psychologist) reviewed and revised the questionnaires and analyzed the database, which was built by several family members using FileMaker Pro 8.5 (FileMaker, Inc., Santa Clara, CA) on the condition of anonymity. The members of the group were informed by a written document of the purpose of the study and were informed that there was no obligation to participate in the study, and that there was protection of anonymity.

The response rate was 88/125 (70%). Participants included four fetuses who died before labor, two fetuses and one participant who died on the day of birth or just before birth, and 81 children including 66 who died and 15 who were alive at the time of this study. Finally, 65 children, whose parents were informed of the karyotypes as full trisomy 18, were included for analysis (Table I). We excluded two children with mosaic trisomy 18, a child with Klinefelter syndrome, and 13 children whose parents were not clearly informed of the karyotypes.

Standard deviation (SD) scores of birth weight, length, and occipitofrontal circumference (OFC) were calculated from the standard growth curves according to sex and gestational ages, produced by the Ministry of Health, Labour and Welfare, Japan. To evaluate factors associated with longer survival, statistical analyses were performed using PASW Statistics 18 for Windows (IBM, Armonk, NY). Children who survived for 1 year and those who did not were compared, excluding Cases 39 and 44 who were <1-year-old and alive at the time of this study. Categorical variables were analyzed by the chi-square test and continuous variables were

TABLE I. Comprehensive List of Children Evaluated

			Pregnancy and delivery				Complications							Management				Outcomes		
										Apnea										
Case number	Survival (days; year(s)/ month(s))	Sex	Prenatal ultrasonographic findings/ karyotyping	Birth weight (g)	Gestational weeks/day (s) at birth	C-section	Congenital heart defect(s)	Other visceral	Skeletal	Apnea	Situation	Severity/ management	Seizures	Policy	Medications	Mechanical ventilation	Oral feeding	Discharge (d, days; w, weeks)	Number of readmission	Cause(s) of death
1	0	F	P,G,B/−	1998	37/2	−	VSD	LS, At, AA, HK, CL	Sy					Li				−		Ap
2	0	M	I,P,G/−	782	30/6	+		RDS, EA, RC	Sy, Po									−		RF
3	0	M	P/−		26	−	HL, IA	EA, AA, HK, HN										−		RF, IAB
4	0	F	I/+	2050	39/0	−	VSD, PA		RH					Li				−		
5	0	M	I,P,H,E/+	1270	35/2	−	DORV	DH/DE						Li				−		HF, RF
6	1	M	I,P,H,G/−	1308	34/0	+	+	EA	Sy					Li		IMV		−		HF
7	4	F	I,P,H,G/+	1544	36/3	−	VSD, PDA	LH, EA						Li		—	NF	−		PH
8	6	M	I/−	1945	39/5	−	VSD, ASD, PDA, CoA, AS	LH						Li		—	NF	−		HF
9	8	M	I,P,G,B/−	2200	41/5	−	VSD, PDA	CL, CP	Sy	+	Sd	St		Li		NC	PO	−		HD
10	8	M	I/−	1920	42	−	VSD, PDA, CoA	HK	TE					Li	Dg, PG	IMV	NF	−		MOF
11	13	F	I,P/+	2074	42/6	−	VSD, ASD, PDA	EA		−				In		IMV	NO	−		RF
12	14	M	I,P/−	1460	38/0	+	VSD	HK		+	Sd	St	Gt(0d)	Li		NC	NO	−		HF
13	18	M	P,H,G,B,E/+	1737	38/3	+		EA, TEF, CL, CP, UT	TE					Li		—	NF	−		HF, RF
14	23	F	I,H/−	2074	42/6	+	VSD, ASD, PDA	WT	Sy				GT			IMV	NO	−		HF
15	27	M	I,P,H,G,E/+	2062	39/4	−	VSD	EA, IH, CL		+	Sd	St		Li		—	NF	−		HF
16	30	F	I/−	1452	35/6	+	VSD, PDA	LH. RDS, CL, CP	Sy					In		IMV		−		PH, PHe
17	31	F	−/−	2270		−	VSD, ASD, PDA			+	Sd	St	GT(26d)			IMV	PO	+(25d)	0	
18	32	F	I,P,G/−	1420	38/1	+	VSD	LH, EA, CL								IMV		−		HF
19	34	F	I,P/−	1338	35	+	VSD, PDA, CoA, DORV	RDS, HK, HN, KF						In		IMV				
20	37	M	I,H,B,E/+	1404	38/1	−	VSD, ASD, PDA, DORV	IH	Po	+	Cr, Sd	St		Li	Di, Xa	—	NO	−		HF
21	57	M	I,P,H,B,E/+	2430	42/1	−	VSD, ASD, PDA, CoA	IH		+		St, MV	GT(34d)	Li	Di, Pb, Se	—	NO	−		HF, RF
22	68	F	I,P,H/−	1990	38/0	+	DORV	0		+	Sl, Sd	Sp		Li		—	PO	−		HF
23	68	F	I/−	1248	36/6	+	VSD, ASD	AA		+	Sl, Cr	St		Li	Di, Xa	—	NO	−		HF
24	73	F	I/−	1682	38/5	+	VSD, ASD			−				Li	Ct, Di	IMV	PO	−*		HF
25	75	F	I/−	1994	42/0	+	VSD, PDA		RH	−					Ct, Di, Se	IMV	NO	−		
26	75	M	I,P,E/+	1450	35/5	+	VSD, ASD, PDA	LH, LS, At	Sy	+	Sd	MV	GT(10d)	In	De, Di, Pb	IMV	NO	−		PH
27	83	F	I/−	1630	35/6	+	VSD, ASD, PDA, CoA, DORV, HL	0, CL		−				In		IMV		−		HF
28	84	F	I,H,B/+	1540	39/5	−	VSD, ASD, PDA	HN		−				In	Di, Ab	—	PO	+(10d)	1	HF, LRI

(*Continued*)

TABLE I. (*Continued*)

			Pregnancy and delivery				Complications							Management					Outcomes		
										Apnea											
Case number	Survival (days; year(s)/ month(s))	Sex	Prenatal ultrasonographic findings/ karyotyping	Birth weight (g)	Gestational weeks/day (s) at birth	C-section	Congenital heart defect(s)	Other visceral	Skeletal	Apnea	Situation	Severity/ management	Seizures	Policy	Medications	Mechanical ventilation	Oral feeding	Discharge (d, days; w, weeks)	Number of readmission	Cause(s) of death
29	88	M	I,P,G/–	1512	34/4	+	VSD, ASD	EA	RH	–				In	Di	IMV	NO	+(55d)	0	RF
30	89	F	I/–	2228	41/1	+	VSD, ASD	HN		–				Li	Di, Se	–	PO	–*		HF
31	98	F	I/–	2108	39	+	VSD, ASD	0	Sy	+	SI, Cr	Sp, MV		In		NC	NO	–		LRI
32	107	F	I/–	1254	35/6	+	VSD, ASD, PDA, CoA	0, OMF, HN, HU	Sy	+	SI, Cr, Sd	Sp, St		In	Di	IMV	PO	–		HF
33	107	F	I,B/+	1512	39/1	–	VSD, ASD		Sy	+	SI	Sp		Li	Di	–	NO	+(49d)	2	HF
34	137	F	I,P,H,B,E/–	1534	37/2	+	VSD, PDA			+				Li	Di	NC	NO	–		Inf
35	146	M	I,H,B/–	2140	43/3	–	VSD, ASD, PDA	IH	RH	–				Li	Dg, Di	–	NO	+(38d)	0	HF
36	164	M	I/–	2026	41/6	–	VSD, ASD, PDA, PS		RH	–				Li	Di, BB, VD	–	NO	+(91d)	1	HF, RF
37	179	F	I,P,H/–	2028	38/3	+	VSD, DORV	RDS		–				Li	Dg, Di, Ex	IMV	NO	+(113d)	0	RF
38	182	M	P,H,G/–	1612	35	+	VSD			+		St	GT			IMV	NO	–		HF, LRI
39	185L	F	I,P/–	1980	37/4	+	VSD, PA		Sy	–				In	PG, ASA, La	IMV	NO	–		
40	196	F	I,P/–	2090	40/4	–	VSD, PDA, CoA		Sy	+		Sp		Li		–	NO	+		HF
41	206	F	–/–	1964	39/4	–	VSD, PDA		Sy						Ct, Ac	–	NO	+(16w)	0	HF
42	233	F	–/–	2650	40	+	VSD			+	SI	St		Li		–	NO	–		Ap
43	236	F	H/–	1986	40/0	–	VSD, CoA	AA								–	PO	+(45d)	1	HF, URI.RF
44	249L	F	–/–	1538	37	+	VSD			–				Li	Di, Ch	NC/IMV	FO	+(16w)	0	
45	249	M	I/–	2290	41/6	–	VSD	LH, IH		+	SI	Sp, St	GT(2m)	Li	Dg, Di	–	PO	+(14d)	1	HF
46	298	F	I,H,G/–	1904	37	+	VSD, ASD, PDA	0		–				In		IMV	NO	–		SCA
47	343	F	I/–	1780		–	VSD, ASD, PDA	HN	RH	–					Ct, Di	IMV	NO	+		HF
48	1/0	M	–/–	2754	39/0	+	VSD, ASD, PDA	TS, IH		+	Cr	St		In	Dg, De, Di, Ub, Th	IMV	PO	+(52d)	1	HF
49	1/0L	F	I,H/–	2050	39/3	+	VSD, PDA	At, 0, GER		–						IMV	NO	–		
50	1/1	F	–/–	2116	42	+	VSD	HB		+	Sd			In	Dg, Di	IMV	PO	+(57d)	2	HB, RF
51	1/5	F	–/–	2812	41/2	–	VSD, ASD, PDA		RH	+	SI	Sp	GT(3m)	In	Di, Pb, BS, Ex, Aa	–	FO	+(35d)	4	LRI
52	1/7L	F	I/–	2316	41	+	VSD, PDA, CoA								Di	–	PO	+(33d)	6	
53	1/10	F	I,P/–	2625	42/1	+	VSD, PDA	IH		–						–	FO	+(34d)	0	Sep
54	2/3	F	I,P/–	1490	38/3	+	VSD	AA, HK		–				Li		–	PO	+(6w)	3	HF
55	2/11L	F	I,P,B,E/–	2198	40/3	–	TOF			+	SI	Sp		Li	BB, Pb, Ex, V	–	PO	+		
56	3/0L	F	I,P/–	1414	37/0	+	VSD, ASD	DH/DE, HH, GER, IH, SUP	Sy, TE	+	SI		GT,P(8m)	In	SRA, PPI, SoB	–	PO	+(93d)	2	
57	3/2	M	I/–	2010	42/4	–	ASD			–			GT(2y)	Li		–	FO	+	7	HF, Cv
58	3/2	F	I/–	1828	41/1	–	VSD		HD	–				Li	Dg, Di	–	PO	+(6w)	0	HF, URI, Ap
59	3/4	F	I/–	2036	41/1	+	VSD, DORV, PS	IH	SD	+	SI		GT(1y)	In	Dg, Di, Xa, Pot, La	IMV	PO	+	2	HF, LRI, Sz
60	9/1	F	I/–	1960	40/5	+	VSD, ASD, CoA		TE, Sc	+	SI	Sp, St		Li	Di, SRA, VD	IMV	PO	+(49d)	33	HF, Inf
61	9/6	F	–/–	2530	42/3	+	VSD, PDA			–				In		IMV	FO	+	>10	HF, LL
62	10/1L	F	–/–	3192	42/1	+	VSD			–				Li		–	FO	+(22d)	0	

(*Continued*)

TABLE I. (*Continued*)

				Pregnancy and delivery				Complications					Apnea		Management				Outcomes		
Case number	Survival [days; year(s)/ month(s)]	Sex	Prenatal ultrasonographic findings/ karyotyping	Birth weight [g]	Gestational weeks/day [s] at birth	C-section	Congenital heart defect(s)	Other visceral	Skeletal	Apnea	Situation	Severity/ management	Seizures	Policy	Medications	Mechanical ventilation	Oral feeding	Discharge [d, days; w, weeks]	Number of readmission	Cause(s) of death
63	10/4L	F	I,P/–	1456	35/2	+	PDA	LH, At, LM	Sy	–			GT[11w]		Di, Pb, Ch, VD	IMV	NO	–		
64	12/4L	F	–/–	2560	41/1	–		DE		–				In		–	FO	+[4w]	Many	
65	26/4L	M	–/–	2460		–	VSD, CoA		Sy							–	FO	+		

Blank, not described; +, present; –, absent; *, temporary return to home; AA, anal atresia; Aa, antiallergic agent; Ab, antibiotics; Ac, anticonvulsant; Ap, apnea; AS, aortic stenosis; ASA, acetyl salytylic acid; ASD, atrial septal defect; At, atelectasis; B, brain malformation; BB, beta blocker; BS, beta stimulant; Ch, chalybeate; CL, cleft lip; CP, cleft palate; CoA, coarctation of aorta; Cr, after crying; Ct, cardiotonic agents; DE, diaphragmatic eventration; De, denopamine; Dg, digoxin; DH, diaphragmatic hernia; Di, diuretics; DORV, double outlet right ventricle; E, external anomaly; EA, esophageal atresia; Ex, expectorant; F, female; FO, full oral feeding; G, gastrointestinal malformation; GER, gastroesophageal reflux; H, heart defect; HB, hepatoblastoma; HD, congenital hip dislocation; HF, heart failure; HK, horseshoe kidney; HL, hypoplastic left heart; HN, hydronephrosis; HU, hydroureter; I, intrauterine growth retardation; IA, interruption of aorta; IAB, intraabdominal hemorrhage; IH, inguinal hernia; IMV, intermittent mandatory ventilation; In, intensive treatment; Inf, infection; KF, kidney failure; L, alive at the time of this study; La, lactobacillus preparation; LH, lung hypoplasia; Li, limitation of treatment; LL, lung lesion; LM, laryngomalacia; LRI, lower respiratory tract infection; LS, abnormal lung segmentation; M, male; MOF, multiple organ failure; MV, recovery by mandatory ventilation; NC, nasal continuous positive airway pressure; NF, no enteral feeding; NO, no oral feeding; O, omphalocele; OF, omphalomesenteric fistula; P, polyhydramnios; PA, pulmonary atresia; Pb, phenobarbital; PS, pulmonary stenosis; PDA, patent ductus arteriosus; PG, prostaglandin; PH, pulmonary hypertension; PHe, pulmonary hemorrhage; PO, partial oral feeding; Po, polydactyly; Pot, potassium; PPI, proton pump inhibitor; RC, renal cyst; RDS, respiratory distress syndrome; RF, respiratory failure; RH, radial hypoplasia/aplasia; Sc, scoliosis; SCA, sudden cardiac arrest; SD, skull defect; Sd, suddenly; Se, sedatives; Sep, sepsis; Sl, at sleep; SoB, sodium bicarbonate; Sp, spontaneous recovery; SRA, serotonin receptor agonist; St, recovery by manual stimmulation; SUP, sinus urogenitalis persistence; Sy, syndactyly; Sz, seizure; TE, talipes equinovarus; TEF, tracheoesophageal fistula; Th, L-thyroxin; TOF, tetralogy of Fallot; TS, tracheal stenosis; Ub, ubidecarenone; URI, upper respiratory tract infection; UT, undescended testis; V, vitamine; VD, vitamine D; VSD, ventricular septal defect; WT, Wilms tumor; Xa, xanthine derivatives.

analyzed using the Student's *t*-test with a *P*-value <0.05 as statistically significant.

To investigate parental experience, four open-ended questions were asked: "What is (was) your child's most attractive feature?" (Q1), "When does (did) your child look happy?" (Q2), "When do (did) you feel happy?" (Q3), and "What are (were) the hardest moments of your life with your child?" (Q4). These questions were not sent to the parents whose children did not survive for 1 day, in consideration of their feelings. Classification according to the specific themes was performed by one of the authors (T.K.) for analysis of the answers.

RESULTS

General Information

The answers to the questionnaires for 58 (89%) children were provided by their mothers, for one child (2%) by the father, and for five (8%) children by both parents. Birth dates of the children ranged from 1977 to 2003, with 49/64 (77%) born after 2000. The mean maternal age at delivery was 34.0 years old (n = 65; range, 23–46) and the mean paternal age was 31.8 years old (n = 65; range, 23–41). The mean number of siblings was 1.0 (n = 62; range, 0–4), only one of whom was described to have disabilities. The female ratio was 68% (44/65).

Diagnosis

A total of 11/65 (17%) children had prenatal diagnosis. All received fetal karyotyping based on amniocentesis after fetal abnormalities had been detected through ultrasonography (US). The mean gestational age of amniocentesis was 32.4 weeks and the median age was 33 weeks (n = 8; range, 27–37). The mean gestational age of diagnosis (when the parents were informed of the fetuses' karyotypes) was 33.9 weeks and the median age was 35 weeks (n = 9; range, 28–38). A total of 54/65 (83%) children had postnatal diagnosis. The median age of diagnosis was 14 days (n = 52; range, 0 days–3 years).

Pregnancy

Twenty-seven mothers (42%) were admitted to hospital during pregnancy because of maternal or fetal reasons. The mean length of hospitalization was 3.3 weeks (range, 1 day–8 weeks). There were single and multiple reasons for admission, including preterm labor in nine mothers, polyhydramnios in eight, intrauterine growth retardation (IUGR) in eight, morning sickness in four, and fetal abnormalities in two. Ultrasonographic abnormalities were described in 54/65 (83%) fetuses as follows: IUGR in 48, polyhydramnios in 28, heart defects in 16, gastrointestinal malformations in 11, brain anomalies in 8, and external anomalies in 8.

Delivery

The mean gestational age at delivery was 38 weeks and 6 days (n = 62; range, 26 weeks–43 weeks and 3 days), with 14 (23%) children born before 37 weeks of gestation. A total of 37/65 mothers

(57%) had a cesarean, which was planned in 15 (41%), performed emergently in 18 (49%), and initially planned and then performed emergently in 4 (11%). A cesarean were performed for the following reasons: fetal distress in 17 mothers (46%), seven of whom resulted from labor induction; post-term pregnancy in seven (19%); abnormal labor in seven (19%); a previous cesarean in six (16%); breech presentation in six (16%); IUGR in six (16%); premature rupture of membranes in four (11%); fetal malformation in three (8%); polyhydramnios in two (5%); maternal physical factors in two (5%). Two children who had been diagnosed prenatally were delivered by an emergency cesarean as follows. Case 13 was delivered because of fetal distress and a maternal disorder necessitating two previous cesarean, and Case 26 was delivered because of fetal distress and a parental request.

The mean birth weight was 1,910 g (n = 64; range, 732–3,192 g): 1,942 g for females (n = 44; range, 1,248–3,192 g); 1,839 g for males (n = 20; range, 782–2,754 g). Birth weight of 46/61 (75%) children was less than −2 SD. The mean birth length was 42.3 cm (n = 56; range, 33.5–49 cm): 42.3 cm for females (n = 39; range, 34–47.5 cm); 42.4 cm for males (n = 17; range, 33.5–49 cm). Height of 42/55 (76%) children was less than −2 SD. The mean birth OFC was 31.2 cm (n = 50; range, 25.8–35 cm): 31.1 cm for females (n = 37; range, 25.8–34 cm); 31.4 cm for males (n = 13; range, 26–35 cm). OFC of 10/49 (20%) children was less than −2 SD.

Structural Defects and Medical Complications

Major malformations included heart defects in 62 children, 40 of whom had simple left-to-right shunt defects, such as ventricular septal defect (VSD), patent ductus arteriosus (PDA), and atrial septal defect (ASD). Additionally, 21 children had complex defects, such as coarctation of the aorta and double outlet of right ventricle, other than simple left-to-right shunt defects. Other major malformations included abdominal wall defects in 14 children, such as inguinal hernia and omphalocele; gastrointestinal defects in 13, such as esophageal atresia and anal atresia; renal defects in 12, such as horseshoe kidney and hydronephrosis; lung/tracheobronchial defects in nine, such as lung hypoplasia and abnormal lung segmentation; cleft lip with/without cleft palate in seven; and diaphragmatic defects (hernia/eventration) in three.

Other malformations included skeletal defects in 29 children, such as syndactyly, radial aplasia/hypoplasia, talipes equinovarus, and polydactyly; and ocular defects, such as corneal opacity, megaloglobus, coloboma of the lens, and microphthalmia.

A total of 24/47 (51%) children experienced apnea. Apnea occurred suddenly in 10 children, during sleep in 11, and after crying hard in 5. Apnea recovered spontaneously in 9 children, by manual stimulation in 12, and by mandatory ventilation in 3. Thirteen children experienced seizures, with the median age of onset at 2 months (n = 11; range, 0 days–2 years). The type of seizures appeared to be a generalized tonic seizure in all children. Seizures disappeared in 1/12 (8%) child, improved in 2/12 (17%), persisted with no change in 6/12 (50%), and worsened in 2/12 (17%). Case 57 died of status epileptics, though his seizures had been stable. Excluding two children with natal teeth, the median age of tooth eruption was 15 months (n = 9; range, 9–22 months).

Medical Management

Management policy. Parents of 18/50 (36%) children were offered intensive treatment. Parents of 3/11 (27%) children were offered intensive treatment after prenatal diagnosis.

Respiratory support. A total of 31/60 (52%) children received mechanical ventilation: intermittent mandatory ventilation (IMV) on 26 children, nasal continuous positive airway pressure on four, and both on one. Information of 30 clinical courses of IMV in 24 children was available. Nine (38%) children received IMV from their early neonatal periods until their deaths. Another nine (38%) children were weaned off IMV that had been initiated on the day of birth, with the median age of 35 days (n = 7; range, 0–163 days). A total of 13 (54%) children were weaned off a total of 16 (53%) courses of IMV, with the median duration of the course as 26 days (n = 14; range, 0–186 days). Case 44 was weaned off IMV after tracheostomy was performed at age 13 weeks.

Surgical operations. Nine children had major surgery. Two children had surgery for esophageal atresia: gastrostomy and ligation of the lower esophagus in Case 11; anastomosis of the esophagus in Case 29. Two children had surgical correction for omphalocele (Cases 27 and 46). Two children had cardiac surgery: Blalock–Taussig shunt at the age of 113 days in Case 39; pulmonary artery banding and PDA ligation at the age of 102 days in Case 46. Two children with a survival longer than 10 years had other types of surgery: surgical correction for congenital hip dislocation at the age of 5 years in Case 64; surgical drainage for subdural hematoma at the age of 5 months in Case 65.

Medications. Thirty-one children were on medication. Cardiovascular agents were used in 30 children, including diuretics, such as furosemide and/or spironolactone, and cardiotonic agents, such as digoxin. Central nervous system-related agents were used in eight children, including antiepileptic drugs and sedatives. Respiratory agents were used in six children, including expectorants and xanthine derivatives. Nutrition and metabolism-related agents were used in six children, including alfacalcidol (vitamin D) and a chalybeate. Gastrointestinal agents were used in four children, including cisapride and a lactobacillus preparation.

Early intervention. Nine children, who all survived for 1 year, had early intervention, including physical therapy in eight, occupational therapy in six, speech therapy in two, and feeding therapy in six.

Courses and Prognosis

Development. Developmental achievements were described in 24 children (Supplementary eTable I—see Supporting Information online). Gross and fine motor development was markedly delayed, with the median ages of achievement of "head control" at 19.5 months (n = 6; range, 5–30 months), "roll over" at 20.5 months (n = 8; range, 8–36 months), and "reach and grasp" at 48 months (n = 8; range, 6–36 months). In contrast, an initial social response was mildly delayed, with the median ages of achievement of "gaze" at 3.5 months (n = 16; range, 0–7 months), "look around" at 4 months (n = 16; range, 1–12 months), "social smile" at 4 months (n = 11; range, 3–29 months), and "recognize the mother" at 6 months (n = 6; range, 1–12 months). Initial verbal development

was also mildly delayed, with the median ages of achievement of "laugh" at 5.5 months (n = 8; range, 5–30 months), and "babbling" at 12 months (n = 5; range, 3–36 months). "Unassisted walking" was accomplished by two children: Case 62 at 2 years and 3 months old; Case 65 at 5 years and 9 months old. "Moving by a walker" was accomplished by two children: Case 61 at 3 years old; Case 64 at 8 years old. "Recognizing language" was accomplished by two children: Case 62 at 1 year old; Case 64 at 10 years old.

Feeding. A total of 8/55 (15%) children were fully fed orally, 18/55 (33%) were partially fed orally, 24/55 (44%) were completely gavage fed, and 5/55 (9%) could not be fed enterally. Case 52 had baby food, and Cases 61, 62, 64, and 65 had adult food.

Hospitalization and discharge. A total of 29/64 (45%) children were discharged home, with the median length of the first hospitalization (from their births) at 43.5 days (n = 22; range, 10–113 days). In those who were discharged, 9/25 (36%) children were not admitted thereafter, five (20%) were admitted once, four (16%) were admitted twice, and seven (28%) were admitted more than twice.

Survival. A total of 60/65 (92%) children survived 1 day, 57/65 (88%) survived 1 week, 50/65 (77%) survived 1 month, 35/65 (54%) survived 3 months, 28/65 (43%) survived 6 months, 18/63 (29%) survived 1 year (excluding two children who were alive and <1 year old at the time of this study, because they could survive longer than 1 year after the study), and 10/60 (17%) survived 3 years (excluding five children who were alive and <3-year-old at the time of this study, because they could survive longer than 3 year after the study). The median survival time was 107 days (n = 65, including all living children at the time of this study because all of them survived longer than this median survival time; range, 0 days–26 years and 4 months). A total of 42/44 (95%) girls survived 1 day, 41/44 (93%) survived 1 week, 39/44 (89%) survived 1 month, and 15/42 (36%) survived 1 year. The median survival time was 196 days (n = 43, including living girls who survived this median survival time, and excluding a living girl who was aged less than this median survival time; range, 0 days–12 years and 4 months). A total of 18/21 (86%) boys survived 1 day, 16/21 (76%) survived 1 week, 11/21 (52%) survived 1 month, and 3/21 (14%) survived 1 year. The median survival time was 37 days (n = 21, including a living boy who survived longer than this median survival time; range, 0 days–26 years and 4 months).

Causes of deaths. Causes of deaths were described as single or multiple. A total of 39/51 (76%) children died of cardiovascular complications, including heart failure in 33 children and pulmonary hypertension with/without pulmonary hemorrhage in three. Fifteen (29%) children died of respiratory complications, including respiratory failure in 11 and apnea in three. Ten (20%) children died of infections, including lower respiratory tract infections in five and upper respiratory tract infections in three. Case 42 died of hepatoblastoma and respiratory failure.

Factors related to survival. Results of statistical analyses of clinical variables related to survival are shown in Table II. The female ratio was higher in those who survived 1 year than in those who did not, but this was not significant. The mean gestational week at birth was significantly later and the mean birth weight was significantly heavier in those who survived 1 year than those who did not. The presence of esophageal atresia was significantly associated with shorter survival, whereas the presence of complex

TABLE II. Factors Related to Survival

	Survival <1y	Survival >1y	*P*-value
Characteristics			
Female	60 (27/45)	83 (15/18)	0.076
Mean gestational week at birth (±SD)	38.25 ± 3.38	40.43 ± 2.01	**0.011**
Mean birth weight (g) (±SD)	1814 ± 405	2180 ± 488	**0.004**
Complex congenital heart defects	28 (13/46)	31 (5/16)	0.528
Esophageal atresia	20 (9/45)	0 (0/18)	**0.037**
Apnea	60 (18/30)	40 (6/15)	0.205
Interventions and courses			
Prenatal diagnosis	24 (11/46)	0 (0/17)	**0.022**
Cesarean section	51 (23/45)	67 (12/18)	0.262
Intensive treatment	29 (10/35)	54 (7/13)	0.100
Intermittent mandatory ventilation	45 (18/40)	39 (7/18)	0.664
Extubated	31 (5/16)	86 (6/7)	**0.024**
Full oral feeding	0 (0/35)	39 (7/18)	**0.000**
Discharge	24 (11/45)	89 (16/18)	**0.000**
Causes of death			
Cardiovascular system	78 (32/41)	70 (7/10)	0.433
Respiratory system	29 (12/41)	30 (3/10)	0.621
Infection	12 (5/41)	50 (5/10)	**0.017**

Values are mean ± SD or % (n). Significant *P*-values (<0.05) are shown in bold.

congenital heart defects or apnea was not. Not having a prenatal diagnosis, extubation, being fully fed orally, and being discharged were significantly associated with longer survival. Being offered intensive treatment also appeared to be associated with longer survival, but this was not significant. Having a cesarean or IMV did not appear to be associated with longer survival. Infection was significantly more frequently described as a cause of death in those who survived 1 year than those who did not, whereas cardiovascular or respiratory complications were described in almost the same proportion of children with a longer survival as of those with a shorter survival.

Parental Experience

Of the parents with 65 children who answered most of the quantitative questions, parents of 48 (74%) children also answered the open-ended Q1 and Q2, those of 47 (72%) children answered the Q3, and those of 39 (60%) children answered the Q4. Classification according to the specific themes for each question is shown together with representative answers.

Q1. What is (was) your child's most attractive feature?. All answers for Q1 are shown in Supplementary eTable II (see Supporting Information online). Parents of 29/48 (60%) children described their child's most attractive feature as the "eyes": "*His powerful eyes. When I looked into his eyes, he looked back at me intensely with his vivid eyes …*" (Case 9). Parents of 14/48 (29%) children described their child's most attractive feature as "smiling/laughing": "*His innocent smiles.*" (Case 65). Parents of 12/48 (25%) children described their child's most attractive feature as "mouth/teeth": "*… puckered-up mouth*" (Case 25). Some parents described that their children were full of attractive features: "*Everything … She had a peaceful character, a sense of humor, a toughness that always made her try hard and never give up, and friendliness …*" (Case 60).

Q2. When does (did) your child look happy?. All answers for Q2 are shown in Supplementary eTable III (see Supporting Information online). Parents of 15/48 (33%) children described that their children looked happy when they were "playing": "*… After about 2 years old, she enjoyed pop-up books and a play gym …*" (Case 54); "*… when she is doing what she likes (playing with stickers indoors and slides outdoors).*" (Case 64). Parents of 15/48 (31%) children described that the time that their children looked happy was when they were "hugged": "*… when she was hugged. Her eyes looked vivid and she spoke often.*" (Case 30); "*When she was hugged by me, she looked relaxed and slept soundly.*" (Case 31). Some children enjoyed communication with their families: "*… Before she falls a sleep between us in bed, she smiles happily looking at us in turn many times (mom, dad, mom, dad, …). She also laughs a lot looking into our eyes, when we move her vigorously, read picture books for her, and play with her hands lying beside her.*" (Case 56); "*… when somebody talked to her, sang songs for her, and did something with her …*" (#60); "*… When all our family get together and talk around the table, he seems really happy, looking at everyone's face, making gestures, giving responses, and laughing …*" (Case 65).

Q3. When do (did) you feel happy?. All answers for Q3 are shown in Supplementary eTable IV (see Supporting Information online). Parents of 29/47 (62%) children felt happy all the time or for their children's birth and existence: "*All the time when he lived. Just the fact that I met him. The chance for me to call his name. All the memories we spent together.*" (Case 8). Some of the parents mentioned their children's contribution to bonds between the family members: "*… When she was alive, we were surrounded by a peaceful atmosphere just to spend time with her, which made us feel calm and stop quarreling …*" (Case 60); "*She is the "sun" that binds our family together …*" (Case 64); "*I feel happy almost everyday. He is always in the center of our family.*" (Case 65). Parents of 26/47 (55%) children felt happy when their children do/did something or the parents do/did something: "*… when she showed a beaming smile … when she achieved something new …*" (Case 58); "*… when seeing her daily events that are experienced by every other child, such as digesting milk and getting restless when pooping, which we would not have seen if she had not been born. Every ordinary thing seems fresh to me and makes me feel really happy, which I would not have noticed if she had been born healthy …*" (Case 63).

Q4. What are (were) the hardest moments of your life with your child?. All answers for Q4 are shown in Supplementary eTable V (see Supporting Information online). Parents of 26/39 (67%) children felt hard about the physical condition of their children and related medical care including exhaustion in the home medical care and anxiety for their child's death that might occur in the near future: "*Because the amount of water he could take per day was restricted, we couldn't do anything but hug and dandle him when he cried and fretted. When he didn't stop crying, I was really worried about the stress on his heart … Milk injection every 3 hours was tough. I wanted to sleep soundly all night, but I realized that this would mean that he was not alive anymore. That was a serious dilemma for me.*" (Case 35). Parents of 11/39 (28%) children had a hard time in the context of family implications including burdens of visiting the hospital when their child was admitted, doing housework, or taking care of their sibling(s): "*If she had been our only child, we could have had more time to spare. Actually, her elder and younger sisters were very young and needed a lot of care and attention, so it was all I could do to survive each day somehow, and I couldn't take as good care of them.*" (Case 53). Parents of 6/39 (15%) children did not think that they had a hard time: "*I didn't mind at all how tough it was because he was my son.*" (Case 26); "*I didn't think that I had a hard time, because we knew that the time was limited. I felt so happy to do anything for her, and I wanted to do more and more things …*" (Case 28). Parents of 3/39 (8%) children had difficulty in social interactions, including the inconvenience of public services (Case 56), poor information on children with trisomy 18 and their families (Case 58), and poor understanding of the disease by teachers in school (Case 61). The mother of the longest survivor (Case 65) mentioned her age-related problems: "*The times when I'm not in good shape. The fact that I can't cope with his problems as my tenacity and vigor decrease as I get older.*"

DISCUSSION

This is the second support group-based study on the natural history of trisomy 18. The first support group-based study was reported by Baty et al. [1994a, b] based on data from the Support Organization for Trisomy 18, 13, and Related Disorders (SOFT) (http://www.trisomy.org). Our study presented various clinical information, including development, intervention (cesarean, mechanical venti-

lation, and surgery), statistically significant clinical variables associated with longer survival, and parental experience.

Pregnancy and Delivery

In the current study, only 17% of children had a prenatal diagnosis of trisomy 18, with a mean gestational age of 32.4 weeks, after fetal abnormalities had been detected through US. In Japan, pregnancy termination is not legally allowed for fetal abnormalities, but is allowed for maternal social (e.g., rape), physical, or economical reasons. Realistically, only in cases of high-risk pregnancy, including advanced maternal age, fetal US abnormalities, and possible recurrence of serious genetic diseases, prenatal diagnosis based on amniocentesis or chorionic villi sampling is performed in each institute after careful genetic counseling. Prenatal mass screening of congenital malformations/chromosomal abnormalities/genetic diseases in view of pregnancy termination is considered to be a highly sensitive issue that should be seriously discussed. Therefore, maternal serum screening and US screening in the first trimester have not spread throughout the country.

Medical Complications

Most of the structural defects described in this study have been listed in previous reviews [Jones, 2006; Carey, 2010]. Several characteristics of apnea in children with trisomy 18 have been demonstrated in this study, which have not been systematically described in spite of its clinical importance as the most common cause of death [Embleton et al., 1996]. Approximately half of the children were shown to have apnea in various situations (suddenly, at sleep, or after crying) and with various severities (spontaneous recovery, manual stimulation, or mandatory ventilation was required).

Many children experienced seizures and the majority was not seizure-free. Surviving children with trisomy 18 should be investigated for seizures, even with minor signs, such as apnea. Intensive evaluations to differentiate epileptic apnea from central apnea are recommended for children presenting with apnea, because caffeine and theophylline, major medications for central apnea, could precipitate epileptic seizures in those with epileptic apnea [Kumada et al., 2010].

Development

Developmental achievements observed in this study (Supplementary eTable I—See Supporting Information online) support the findings by Baty et al. [1994b] that children with trisomy 18 achieve some psychomotor maturation and continued to learn, although they show severe to profound developmental disability. In particular, four long-term survivors over the age of 10 years showed remarkable physical and psychosocial maturation. Two of these survivors walked independently, one moved with a walker, three were fully fed orally, two recognized language, one took care of an infant, and one sang a lot of songs with gestures. Possibilities of mosaicism could not be excluded, because none of the children were reported to have karyotyping using cells other than peripheral blood lymphocytes, such as skin fibroblasts.

To our knowledge, there have been two reports describing children with full trisomy 18 who walked unassisted. One is a 20-year-old girl at the time of publication by Ray et al. [1986], who began to walk unassisted at age 1 year and 8 months. Chromosomal analysis of skin fibroblasts as well as leukocytes revealed no evidence of mosaicism. The other is a 10-year-old girl at the time of publication by Kajiwara et al. [2004], who began to walk unassisted at age 2 years and 6 months. At age 8 years, intelligence quotient was 38 and social intelligence quotient was 54. Chromosomal analysis using leukocytes at age 0 days (20 cells) and again 4 years old (50 cells) revealed no evidence of mosaicim.

Management Policy, Survival, and Survival-Related Factors

In the current study, the parents of 36% of the children were offered intensive treatment. A substantial number of the children, whose parents were offered limitation of treatment, actually had intensive treatment, including mechanical ventilation, tracheostomy, and various medications (Table I). This could be the reason why this series showed a longer survival than previous population-based studies. Therefore, our finding could provide evidence that standard neonatal to pediatric intensive management is an important factor for a longer survival, as illustrated by Kosho et al. [2006]. Japanese pediatricians' attitudes toward children with severe disorders and/or disabilities, such as those with trisomy 18, appear to be remarkable in their positiveness to intensive treatment. These attitudes might be supported by a secure national health insurance system covering almost all costs of treatment for every sick child, general respect for life, and the families' strong wishes to prolong the children's lives [Sakakihara et al., 2000; Kosho et al., 2006]. In our clinical experience, it appears to be natural for Japanese pediatricians, nurses, clinical psychologists, early intervention therapists, and other co-medical staffs treating children with severe disorders and/or disabilities to consider the children's existence itself to be precious, and their developmental maturation, even if they are tiny, to be highly valuable.

To date, only the study by Rasmussen et al. [2003] performed statistical analyses of survival of children with trisomy 18 and its associated factors. Male sex and white ethnicity were associated with a shorter survival at 1 month, although sex was not a predictor of survival at 1 year. Congenital heart defects were not associated with decreased survival. In our study, diagnosis only after birth, longer gestational weeks, heavier birth weight, absence of esophageal atresia, ability to feed orally without medical assistance, and home discharge were significantly associated with a longer survival over 1 year. Female sex and being offered intensive treatment also appeared to be associated with a longer survival, but this was not significant.

Parental Experience

In our study, the parents appeared to be positive about caring for their children and the children seemed to interact with parents and siblings for as long as they lived, which resulted in quality time. The most common issue that the parents found difficult was the physical condition of their children and related medical care (exhaustion

from home medical care and anxiety for the future of their children). In a recent study by Janvier et al. [2012], who surveyed parents of children with trisomy 13 or 18 who belong to social networks, almost all the parents reported that their child with the syndrome enriched their life. They also found that most of the parents who had other children felt that their child with trisomy 13 or 18 had a positive effect on siblings, and approximately two thirds of the parents stated that this child had a positive effect on the relationship between the mother and the father. The most common negative comment was a sense that healthcare providers did not see their child as having value, as being unique, and as being a baby but a syndrome. Walker et al., [2008] investigated the health-care experiences of families given the prenatal diagnosis of trisomy 18 who were recruited through the Trisomy 18 Foundation online parent support program (http://www.trisomy18.org) and from the University of Michigan Perinatal Assessment Center. They found that family satisfaction depends on expression of empathy from providers, continuity of care, communication, valuing the fetus, and participation in medical decision-making. Parent completed data described by the Tracking Rare Incidence Syndromes (TRIS) project (http://web.coehs.siu.edu/Grants/TRIS/) reported that children with trisomy 18 were aware of their surroundings, had a positive quality of life, and had positive impact on others [Bruns, 2010]. Several individual experiences have also been published to illustrate parental unconditional love irrelevant to the length of their child's life, even when the child die in utero, and siblings' voluntary and self-sacrificing attitudes, as well as difficulty in having a relationship with healthcare providers [Farlow, 2008; Thiele, 2010]. Similarly, Skotko et al. [2011a, b] surveyed families of individuals with Down syndrome using the mailing lists of six nonprofit Down syndrome organizations, and found that almost all the parents loved their son or daughter with the syndrome and were proud of him or her, and most of the parents thought that their outlook on life was positive. The vast majority of brothers and sisters considered their relationship with their sibling with Down syndrome as positive and enhancing. Such parental perspectives appear to be universal beyond the generation and severity of the disorders.

Limitations

This study contains inevitable limitations as follows:

1. Medical information might have been inaccurate. In contrast to the study by Baty et al. [1994a, b], we did not refer to medical records of each child. We attached greater importance to clinical information easily recognized by parents than to findings recognized through specific medical tests.
2. Selection bias might have been present. Our study did not contain a representative sample of children with trisomy 18. Longer survival in this series than previous population-based studies suggests that this cohort might have included milder children than the general population with trisomy 18. However, motives of parents for joining the support group and participating in this study might be variable. Therefore, we do not know whether this study overestimated (including a severer population) or underestimated (including a milder population) the severity of the syndrome. We present a list of comprehensive characteristics of the children (Table I), so that the readers can determine the quality of the data in connection with severities of complications and the type of interventions. As a result, the survival figure was similar to that in a typical institutional study in Japan providing standard neonatal intensive care without cardiac surgery [Kosho et al., 2006], which is compatible with a considerable number of children receiving intensive treatment in this study.
3. There might have been recall bias. It might be difficult for parents with long-term survivors to recall information, especially that in the neonatal period longer than 5 years before the survey completion. However, these parents could recount detailed information and describe meaningful experiences, which give breadth and depth to this study, as commented by Bruns in the TRIS study [2010].
4. The time of the study could have affected the results. Approximately three-fourths of the children evaluated in this study were born from 2000 to 2003. Since then, management of fetuses or children with trisomy 18 in Japan appears to have changed. First, prenatally diagnosed cases might have increased because of establishment of regional perinatal centers all over the country. Second, more institutes might have adopted neonatal intensive treatment, including mechanical ventilation and surgery because of activities of the "Trisomy 18 Support Group in Japan", publication about such intensive management [Kosho et al., 2006; Kaneko et al., 2008, 2009; Matsumoto et al., 2008; Maeda et al., 2010], and the establishment and spread of the "Guidelines for Healthcare Providers and Parents to Follow in Determining the Medical Care of Newborns with Severe Disease" (http://plaza.umin.ac.jp/%7Ejspn/guideline.pdf). The guidelines present a general principle to cope with families of neonates with severe disorders and/or disabilities through frank discussion and equal communication for seeking the "best interests of the babies" [Kosho, 2008]. If this questionnaire-based study is conducted again at present, we do not know whether these changes can have a positive or negative impact on the results, especially the rate of a cesarean and intensive management, as well as the overall survival.

Implications

In this second support group-based study from Japan, where intensive treatment for children with trisomy 18 is now recognized as a reasonable option of management, we outlined the natural history and parental experience of the disorder. We observed that children in this series had typical major malformations and severe complications. Half of the mothers had a cesarean. One-third of the families were offered intensive treatment. Half of the children received IMV, which were weaned off in half of them. Half of the children were discharged home from the first hospitalization. A total of 29% survived 1 year and the survivors achieved some psychomotor milestones and appeared to interact with their families, and the parents adapted well. These findings taken together with recent evidence of efficacy in neonatal intensive treatment and cardiac surgery [Graham et al., 2004; Kosho et al., 2006; Kaneko et al., 2008, 2009; Maeda et al., 2011], as well as positive parental

feelings [Walker et al., 2008; Bruns, 2010; Janvier et al., 2012], could justify an intensive approach in the care of children with trisomy 18, adjusted to individual physical conditions and considering parental feelings.

Parents having the prenatal diagnosis of trisomy 18 should be greeted with empathy by healthcare providers, have communication with the providers continuously appreciating the value of the fetus, and participate in medical decision-making based on comprehensive information about the natural history of children with the disorder and parental experience, as suggested by Walker et al. [2008]. Parents having the postnatal diagnosis of trisomy 18 should participate in discussion with providers for seeking the best interest of the neonate after stabilization of him/her through necessary resuscitation, as proposed by Carey [2009]. This is in contrast with McGraw and Perlman's view [2008] that such an intervention would diminish the best interest of the neonate. If the parents choose intensive management, then appropriate respiratory, cardiovascular, and nutritional support, as well as prevention of infection, is initiated based on the standard neonatal intensive care protocol and evidence specific to neonatal intensive care and surgery for trisomy 18 [Graham et al., 2004; Kosho et al., 2006; Kaneko et al., 2008, 2009; Maeda et al., 2011]. Sincere discussion with the parents should be continued, and treatment decisions can be made on a day-by-day, week-by-week, or month-by-month basis according to the physical status of the child [Carey, 2010]. Such management, although cumbersome for healthcare providers, is an ordinary approach for neonates/children with severe disorders and/or disabilities, where the providers are used to show respect and humanity to the neonates/children and the parents.

ACKNOWLEDGMENTS

We thank Mrs. Kaori Otani and Mrs. Sonoko Hoshiyama (Trisomy 18 Support Group in Japan) for their support in the collection of the questionnaires, and also thank to Dr. Rie Kawamura and Dr. Yusuke Shimizu (Shinshu University) for their assistance in the preparation of the manuscript. We are particularly grateful to all the families who participated in this study, and also those who could not answer the questionnaires for various reasons. This study was supported by the KITAGAWA Encouragement Award (H.S.), Grants-in-Aid for Young Scientists (#16790607, #18790758) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (T.K.), and Research on Intractable Diseases from the Japanese Ministry of Health, Labour and Welfare (T.K.).

REFERENCES

Baty BJ, Blackburn BL, Carey JC. 1994a. Natural history of trisomy 18 and trisomy 13: I. Growth, physical assessment, medical histories, survival, and recurrence risk. Am J Med Genet 49:175–188.

Baty BJ, Jorde LB, Blackburn BL, Carey JC. 1994b. Natural history of trisomy 18 and trisomy 13: II. Psychomotor development. Am J Med Genet 49:189–194.

Bos AP, Broers CJ, Hazebroek FW, van Hemel JO, Tibboel D, Wesby-van Swaay E, Molenaar JC. 1992. Avoidance of emergency surgery in newborn infants with trisomy 18. Lancet 339:913–915.

Brewer CM, Holloway SH, Stone DH, Carothers AD, FitzPatrick DR. 2002. Survival in trisomy 13 and trisomy 18 cases ascertained from population based registers. J Med Genet 39:e54.

Bruns DA. 2010. Neonatal experiences of newborns with full trisomy 18. Adv Neonatal Care 10:25–31.

Carey JC. 2009. To the editor. Pediatrics 123:e547–e548.

Carey JC. 2010. Trisomy 18 and trisomy 13 syndromes. In: Cassidy SB, Allanson JE, editors. Management of genetic syndromes, 3rd edition. New York: Wiley-Blackwell. pp 807–823.

Carter PE, Pearn JH, Bell J, Martin N, Anderson NG. 1985. Survival in trisomy 18. Clin Genet 27:59–61.

Embleton ND, Wyllie JP, Wright MJ, Burn J, Hunter S. 1996. Natural history of trisomy 18. Arch Dis Child Fetal Neonatal Ed 75:F38–F41.

Farlow B. 2008. The decision to accept disability: One family's perspective. Paediatr Child Health 13:367.

Goldstein H, Nielsen KG. 1988. Rates and survival of individuals with trisomy 18 and 13. Clin Genet 34:366–372.

Graham EM, Bradley SM, Shirali GS, Hills CB, Atz AM, Pediatric Cardiac Care Consortium. 2004. Effectiveness of cardiac surgery in trisomies 13 and 18 (from the Pediatric Cardiac Care Consortium). Am J Cardiol 93:801–803.

Janvier A, Farlow B, Wilfond BS. 2012. The experience of families with children with trisomy 13 and 18 in social networks. Pediatr 130:293–298.

Jones KL. 1988. Trisomy 18 syndrome. In: Jones KL, editor. Smith's recognizable patterns of human malformation, 4th edition. Philadelphia: W.B. Saunders. pp 16–19.

Jones KL. 2006. Trisomy 18 syndrome. In: Jones KL, editor. Smith's recognizable patterns of human malformation, 6th edition. Philadelphia: Elsevier Saunders. pp 13–17.

Kajiwara M, Teshima C, Miyawaki T, Takeuchi T, Sonoda K, Inoue K, Iida K, Tamai Y, Iwamatsu H, Inoue T. 2004. Trisomy 18 in a 10-years old girl. J Jpn Pediatr Soc 108:1230–1233 (in Japanese).

Kaneko Y, Kobayashi J, Yamamoto Y, Yoda H, Kanetaka Y, Nakajima Y, Endo D, Tsuchiya K, Sato H, Kawakami T. 2008. Intensive cardiac management in patients with trisomy 13 or trisomy 18. Am J Med Genet Part A 146A:1372–1380.

Kaneko Y, Kobayashi J, Achiwa I, Yoda H, Tsuchiya K, Nakajima Y, Endo D, Sato H, Kawakami T. 2009. Cardiac surgery in patients with trisomy 18. Pediatr Cardiol 30:729–734.

Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, Hazinski MF, Halamek LP, Kumar P, Little G, McGowan JE, Nightengale B, Ramirez MM, Ringer S, Simon WM, Weiner GM, Wyckoff M, Zaichkin J. 2010. Part 15: Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122: S909–S919.

Kosho T, Nakamura T, Kawame H, Baba A, Tamura M, Fukushima Y. 2006. Neonatal management of trisomy 18: Clinical details of 24 patients receiving intensive treatment. Am J Med Genet Part A 140A:937–944.

Kosho T. 2008. Invited comment: Care of children with trisomy 18 in Japan. Am J Med Genet Part A 146A:1369–1371.

Kumada T, Nishii R, Higashi T, Oda N, Fujii T. 2010. Epileptic apnea in a trisomy 18 infant. Pediatr Neurol 42:61–64.

Maeda J, Yamagishi H, Furutani Y, Kamisago M, Waragai T, Oana S, Kajino H, Matsuura H, Mori K, Matsuoka R, Nakanishi T. 2011. The impact of cardiac surgery in patients with trisomy 18 and trisomy 13 in Japan. Am J Med Genet Part A 155A:2641–2646.

Matsumoto N, Koga H, Takahashi M, Iida K, Kajiwara M. 2008. Changes in treatment of trisomy 18 in the NICU. J Jpn Soc Perinat Neonat Med 44:39–42 (in Japanese).

McGraw MP, Perlman JM. 2008. Attitudes of neonatologists toward delivery room management of confirmed trisomy 18: Potential factors influencing a changing dynamic. Pediatrics 121:1106–1110.

Merritt TA, Catlin A, Wool C, Peverini R, Goldstein M, Oshiro B. 2012. Trisomy 18 and trisomy 13: Treatment and management decisions. NeoReviews 13:e40–e48.

Naguib KK, Al-Awadi SA, Moussa MA, Bastaki L, Gouda S, Redha MA, Mustafa F, Tayel SM, Abulhassan SA, Murthy DS. 1999. Trisomy 18 in Kuwait. Int J Epidemiol 28:711–716.

Nembhard WN, Waller DK, Sever LE, Canfield MA. 2001. Patterns of first-year survival among infants with selected congenital anomalies in Texas, 1995–1997. Teratology 64:267–275.

Niedrist D, Riegel M, Achermann J, Schinzel A. 2006. Survival with trisomy 18—Data from Switzerland. Am J Med Genet Part A 140A:952–959.

Nishida H, Yamada T, Arai T, Nose K, Yamaguchi K, Sakamoto S. 1987. Medical decision making in neonatal medicine. J Jpn Soc Perinat Neonat Med 23:337–341 (in Japanese).

Nolan JP, Soar J, Zideman DA, Biarent D, Bossaert LL, Deakin C, Koster RW, Wyllie J, Böttiger B, ERC Guidelines Writing Group. 2010. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. Resuscitation 81:1219–1276.

Rasmussen SA, Wong LYC, Yang QY, May KM, Friedman JM. 2003. Population-based analysis of mortality in trisomy 13 and trisomy 18. Pediatr 111:777–784.

Ray S, Ries MD, Bowen JR. 1986. Arthrokatadysis in trisomy 18. J Pediatr Orthop 6:100–102.

Rochelson BL, Trunca C, Monheit AG, Baker DA. 1986. The use of a rapid in situ technique for third-trimester diagnosis of trisomy 18. Am J Obstet Gynecol 155:835–836.

Root S, Carey JC. 1994. Survival in trrisomy 18. Am J Med Genet 49:170–174.

Sakakihara Y, Masaya K, Kim S, Oka A. 2000. Long-term ventilator support in patients with Werdnig–Hoffmann disease. Pediatr Int 42:359–363.

Schneider AS, Mennuti MT, Zackai EH. 1981. High cesarean section rate in trisomy 18 births: A potential indication for late prenatal diagnosis. Am J Obstet Gynecol 140:367–370.

Skotko BG, Levine SP, Goldstein R. 2011. Having a son or daughter with Down syndrome: Perspectives from mothers and fathers. Am J Med Genet Part A 155A:2335–2347.

Skotko BG, Levine SP, Goldstein R. 2011. Having a brother or sister with Down syndrome: Perspectives from siblings. Am J Med Genet Part A 155A:2348–2359.

Thiele P. 2010. He was my son, not a dying baby. J Med Ethics 36:646–647.

Vendola C, Canfield M, Daiger SP, Gambello M, Hashmi SS, King T, Noblin SJ, Waller DK, Hecht JT. 2010. Survival of Texas infants born with trisomies 21, 18 and 13. Am J Med Genet Part A 152A: 360–366.

Walker LV, Miller VJ, Dalton VK. 2008. The health-care experiences of families given the prenatal diagnosis of trisomy 18. J Perinatol 28:12–19.

Young ID, Cook JP, Mehta L. 1986. Changing demography of trisomy 18. Arch Dis Child 61:1035–1036.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Table I. Developmental achievements.

Table II. Parental experiences of their children with trisomy 18.

Table III. Parental experiences of their children with trisomy 18.

Table IV. Parental experiences of their children with trisomy 18.

Table V. Parental experiences of their children with trisomy 18.