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ORIGINAL ARTICLE

Clinical courses of children with trisomy 13 receiving intensive neonatal and pediatric treatment

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Management of children with trisomy 13 (T13) is controversial because of a paucity of evidence of the natural history, especially focusing on efficacy of treatment. There has been no report regarding natural history of children with T13 receiving intensive neonatal and pediatric treatment without cardiac surgery, although several reports have suggested efficacy of cardiac surgery. To describe the detailed and comprehensive natural history of children with T13 receiving intensive neonatal and pediatric treatment without cardiac surgery, we reviewed clinical information of 24 children with full T13 (15 boys, 9 girls) who were admitted to Nagano Children's Hospital from 1994 to 2016. Intensive neonatal and pediatric treatment without cardiac surgery was provided through careful discussion with the parents. We detailed accurate frequencies of complications, survival, underlying factors and the final modes of death, and psychomotor development of survivors. Unpublished complications including aortopulmonary window, pulmonary-ductus-descending aorta-trunk, biliary system abnormalities, eosinophilic enteritis, and neuroblastoma were described. Accurate frequencies of congenital heart defects (92%) and laryngomalacia and/or tracheomalacia (42%) were determined. The median survival time was 451 days and the 1-year survival rate was 54%. The major underlying factor associated with death was congenital heart defects and heart failure (63%) and the major final mode of death was heart failure (50%). Long-term survivors appeared to show slow but constant psychomotor development. Intensive neonatal and pediatric treatment without cardiac surgery for children with T13 is efficient for survival and psychomotor development, and could be a reasonable choice for parents having fetuses or children with T13.

KEYWORDS

causes of death, intensive treatment, psychomotor development, natural history, survival, trisomy 13

1 | INTRODUCTION

Trisomy 13 (T13) is the third most common autosomal trisomy syndrome in live-born infants. T13 is characterized by craniofacial features, various visceral, skeletal, ocular, and brain malformations, visual and hearing impairment, a short lifespan, and severe developmental delay in survivors (Carey, 2010; Jones, 2013). The largest and the most commonly cited population-based study on T13 showed a 1-year survival rate of 5.61–8.6% and the median survival time was 7–10 days (Rasmussen, Wong, Yang, May, & Friedman, 2003), and the recent population-based study showed a 1-year survival rate of 11.5%, similar to trisomy 18 (T18) (Meyer et al., 2016). The major causes of death were reported as apnea and withdrawal of treatment (Wyllie, Wright, Burn, & Hunter, 1994), and the presence of a congenital heart defect was not shown to be associated with early death (Rasmussen et al., 2003).

Management of children with T13 is controversial (Carey, 2012). Intensive treatment (cesarean section, resuscitation, respiratory support, and surgical procedures) was recommended to be withdrawn because of the short life span and severe developmental delay (Goldstein & Nielsen, 1988; Jones, 1988; Wyllie et al., 1994). Recent neonatal intensive care has placed considerable emphasis on parental decision-making in the context of the best interest of the child (Carey, 2010; Jones, 2013). Although cardiac surgery has been suggested to

be efficient (Graham et al., 2004; Kaneko et al., 2008; Maeda et al., 2011), the efficacy of intensive neonatal and pediatric management without cardiac surgery has not been described. Previously, we demonstrated efficacy of intensive neonatal treatment without cardiac surgery (Kosho et al., 2006) and surgery for esophageal atresia (Nishi et al., 2014) on survival of children with T18 from experiences in Nagano Children's Hospital. This hospital is a tertiary prefectural hospital for sick children in Japan, where intensive neonatal and pediatric management without cardiac surgery is routinely provided to children with T18 or 13. This study aimed to investigate detailed and comprehensive clinical information of children with T13, who had intensive neonatal and pediatric management without cardiac surgery.

2 | MATERIALS AND METHODS

2.1 | Study data

We evaluated 24 children with full T13 (15 boys, 9 girls), who were admitted to Nagano Children's Hospital from 1994 to 2016. Children with T18 or T13 were managed under the principle of providing standard intensive neonatal and pediatric treatment through careful discussion with the parents based on evidence from previous literature (Kosho et al., 2006; Nishi et al., 2014). Management comprised resuscitation (e.g., intratracheal intubation), appropriate respiratory support, establishment of enteral nutrition (e.g., corrective and palliative surgery for gastrointestinal malformations), and pharmacological treatment for infection, seizures, and congenital heart defects.

We collected clinical information on prenatal findings, delivery, complications, treatment, survival, and causes of death from medical records. These records were obtained from Nagano Children's Hospital and regional hospitals where children were provided medical care before or after transfer. We also obtained information on growth, development, and feeding in some children with long-term survival. Detailed information of surgical procedures in these children are described elsewhere (Shibuya et al., 2018).

2.2 | Survival

Comparison of survival of the two groups (e.g., boys with T13 vs. girls with T13) was conducted using Kaplan–Meier survival curves and evaluated with the log-rank test. Continuous variables were analyzed using the Mann–Whitney test and categorical variables were analyzed by the chi-square test. These analyses were performed using SPSS software version 23 (IBM, Armonk, NY). A p value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Prenatal findings and delivery

Data are shown in Table 1. Fetal ultrasonographic abnormalities were detected in 13 (54%) mothers. Five fetuses were diagnosed by karyotyping in amniotic fluid cells. Eight (33%) neonates including two prenatally diagnosed cases (Individuals 1 and 16) were born by cesarean, which was selective in one (Individual 1) and emergent in seven. The common indications for emergent cesarean were fetal distress in six children and rupture of a uterine vein in one. Resuscitation by intubation was required in 20 (83%) children. The mean gestational age was 36 weeks and 6 days and the median was 37 weeks and 2 days (range, 29 weeks and 1 day–39 weeks and 6 days). The mean birth weight was 2273 g and the median was 2230 g (range, 690–3758 g). The mean Apgar score was 4.7 and the median was five (range, 1–9) at 1 min. The mean Apgar score was 6.8 and the median was seven (range, 2–10) at 5 min.

3.2 | Structural defects and medical complications

Data of structural defects and complications are shown in Table 1. Twenty-two (92%) children had congenital heart defects, including ventricular septal defect (n = 9, 38%), patent ductus arteriosus (n = 9, 38%), atrial septal defect (n = 8, 33%), double outlet right ventricle (n = 6, 25%), pulmonary atresia (n = 3, 13%), coarctation of the aorta (n = 2, 8%), patent foramen ovale (n = 2, 8%), and a small left ventricle (n = 2, 8%). Nine (38%) children had simple left to right shunt defects and 12 (50%) had complex defects. Twelve (50%) children developed pulmonary hypertension.

Sixteen (67%) children had gastrointestinal complications, including gastroesophageal reflux (n = 7, 29%), cholestasis (n = 5, 21%), bile stones (n = 2, 8%), and intestinal malrotation (n = 2, 8%). One child (Individual 24), diagnosed with eosinophiric enteritis by biopsy, had central venous nutrition for malnutrition.

Eleven (46%) children showed apnea. Ten (42%) children had laryngomalacia and/or tracheomalacia diagnosed through clinical and endoscopic findings, which resulted in respiratory failure. One child (Individual 15) who had eventration of the diaphragm needed plication surgery and another (Individual 22) showed chronic lung disease.

Twelve (50%) children showed brain anomalies, including cerebellar hypoplasia (n = 5, 20%), colpocephaly (n = 4, 17%), and holoprosencephaly (n = 3, 13%). Nine (38%) children showed epilepsy and were treated with antiepileptic drugs. One child (Individual 12) with polymicrogyria developed a single seizure and another (Individual 13) had an electroencephalogram with spikes and waves, both of whom were not treated.

Seventeen (71%) children had genitourinary complications, including cryptorchidism (n = 8, 53% of boys), hydronephrosis (n = 6, 25%), micropenis (n = 5, 33% boys), polycystic kidney (n = 4, 17%), and bilateral vesicoureteral reflux (n = 2, 8%).

Fourteen (58%) children showed endocrinological or metabolic complications. Eight (33%) children had neonatal persistent hypoglycemia, two of whom (Individuals 10 and 20) showed hyperinsulinemia. Five (21%) children had hypothyroidism treated with levothyroxine. Two (8%) (Individuals 22 and 24) children were found to have osteoporosis. Individual 22 had a fracture of the right femur with an age of 4 years after no apparent preceding trauma. One (Individual 16) child with holoprosencephaly showed diabetes insipidus requiring antidiuretic therapy.

Twenty two (92%) children had craniofacial complications, including cleft lip and/or palate (n = 16, 67%), hearing loss (n = 11, 46%), congenital scalp and/or skull defects (n = 7, 29%), congenital cataracts

TABLE 1 Prenatal and perinatal findings, structural defects, and medical complications of patients with T13

		Perinatal findings								*Complications*								
Case	Sex	Gestational age (weeks/days)	Birth weight (g)	Apgar score (1/5 min)	Cesarean section	Resuscitation by intubation	Prental ultrasonographic findings	Prenatal diagnosis by amniocentesis	Karyotype	Cardiovascular	Gastrointestinal	Respiratory	Neurological	Genitourinary	Endochrinological/ metabolic	Craniofacial	Musculosleletal	Others
1	F	38w0d	1882g	7/8	+	+	CHD, CL, CP, CH	+	47,XX,+13	DORV, PA, PDA	CS	TM	CH		HTH	CLP		SE
2	F	36w2d	2128g	4/6	+	+	IUGR, CHD		47,XX,+13	PDA, PFO	–	–	CH			CSD, HL, IC		
3	F	35w3d	1528g	2/7	+	+			47,XX,+13	TVD	OM, GER	AP	CCE			CP	PD	
4	M	37w2d	1778g	3/7		+	IUGR, OH		47,XY,+13	IAA, APW, VSD, HT, PDDT, PH	OM					CLP, HL	PD	PN
5	F	38w6d	2830g	2/6		+			47,XX,+13	DORV, VSD, PA, PDA	CS, GER	TM, AP			HG	CLP	PD	PN
6	M	38w4d	3758g	8/8		–			47,XY,+13	–	–	–		CO	AT	CSD, CLP, HL	PD	NB
7	M	39wld	2808g	5/6		+			47,XY,+13	VSD, PH	BS, CA	TM	CH	CO		CSD, CLP, MO, COP	PD	SE
8	M	37w2d	2758g	4/2		+	CL, CP, HN		47,XY,+13	PDA, PH, PPHN	–	–	CCE	CO, HK		CLP	PD	SE
9	F	38w2d	1690g	5/8	+	+	IUGR, OHA, MH		47,XX,+13	DORV, VSD, SLV, MS, PH	CS, BS, GER	TM		HN	HG			UTI
10	F	37w0d	1834g	2/6	+	–	IUGR		47,XX,+13	CoA, VSD, PDA, PFO, PPS, BAV	CS, IM	LM, TM	CCE	HN	HG, HTH	HL, CC, CSD, RD	PD	
11	M	35w3d	2020g	7/8		+			46,XY,+13, der(l3;14) (q10 ;q10)	DORV, PA, PH	GER, IP	AP		CO				
12	M	38w3d	3070g	9/10		+	Nucal cord		47,XY,+13	ASD, PH		TM, AP	PM			CLP,HL		PN
13	M	37w4d	2846g	2/8		+			47,XY,+13	ASD, TOF, PDA, SLV		AP		MP, HN		CP	SD	
14	M	36w6d	1884g	8/9		–	IUGR		47,XY,+13	DORV, VSD, PDA, PH		ΛP		MP		CLP	OD, UH	
15	M	34w0d	2288g	4/7		+	CHD, OM, CH	+	47,XY,+13	ASD, PDA, CoA	OM	LM, TM, DM	EP, CH	MP, CO, VUR	HG	CC, CSD, HL, MO	PD	UTI
16	F	29wld	690g	6/7	+	+	CHD, CL, CP, IUGR, HP	+	47,XX,+13	DORV, VSD, PDA, PS	GER	AP	EP, HP	DK, PK	HG, DI	CLP	PD	PN
17	M	36w6d	2052g	5/6		–	HN		47,XY,+13	VSD, ASD	OM	AP		MP, HN, CO	HG	CC, CSD, HL	PD	
18	M	32w6d	1492g	1/3		+	HP	+	47,XY,+13	–	GER	AP	EP, HP	CO		HL, MO	PD	
19	M	36wld	2840g	5/7	+	+			47,XY,+13	ASD, PH		TM, AP	CCE, EP	MP	HTH	CLP, HL, CG		UTI
20	M	39w2d	2624g	6/7	+	+			47,XY,+13	ASD, PH	CS, GER	TM, AP	EP	CO, PK	HG	CC, CP, HL, EAA	PD	SE
21	F	36w5d	2250g	4/8		+	CHD, CP	+	47,XX,+13	VSD	BD	LAM	EP, HP	HN	HG	CLP, HL, CC	PD	
22	M	37w2d	2798g		NA	+			47,XY,+13	ASD, PH	IM	CLD	EP, SDH		HTH, OP	CG		UTI
23	M	39w6d	2210g	5/6		+	CHD, CL, CP, IUGR, CH		47,XY,+13	TA, PH	–	TM	EP, CH	HN, PK VUR	HG	CSD, CLP	PD	UTI
24	F	37w2d	2490g		NA	–			47,XX,+13	ASD, PH, NC	GER, EE	TBA	EP	PK	HTH, OP	CC, CLP, IC	PD	SE, UTI, PN

AP = apnea; APW = AP-window; ASD = atrial septal defect; AT = adrenal tumor; BAV = bicuspid aortic valve; BD = biliary dilatation; BS = bilestone; CA = cholangitis; CC = congenital cataract; CCE = colpocephaly; CG = congenital glaucoma; CH = cerebellar hypoplasia; CHD = congenital heart defect; CLD = chronic lung disiase; CL = cleft lip; CLP = cleft lip and palate; CO = cryptorchism; COP = corneal opacity; CP = cleft palate; CS = cholestasis; CSD = congenital scalp and/or skull defect; DE = diaphragmatic eventration; DI = diabetes insipidus; DK = duplex kidney; DORV = double-outlet right ventricle; EAA = external auditory canal atresia; EE = eosinophilic enteritis; EP = epilepsy; GER = gastroesophageal reflux; HG = neonatal persistent hypoglycemia; HK = horseshoe kidney; HL = hearing loss; HN = hydronephrosis; HT = hemitruncus; HTH = hypothyroidism; IAA = interrupted aortic arch; IC = iris coloboma; IM = intestinal malrotation; IP = ileal perforation; IUGR = intrauterine growth retardation; LM = laryngomalacia; MH = Myocardial hypertrophy; MP = micropenis; MO = microphthalmia; MS = mitral value stenosis; NB = Neuroblastoma; NC = non-compaction myocardium; OD = oligodactyly; OH = oligohydroamnios; OM = omphalocele; OP = osteoporosis; PA = pulmonary atresia; PD = polydactyly; PDA = patent ductus arteriosus; PDDT = pulmonary-ductus-descending aorta-trunk; PFO = patent foramen ovale; PH = pulmonary hypertension; PK = polycystic kidney; PM = polymicrogyria; PN = pneumonia; PPHN = persistent pulmonary hypertension of the newborn; RD = retinal detachment; SD = Syndactyly; SDH = subdural hematoma; SE = sepsis; SLV = small left ventricle; TA = truncus arteriosus; TBA = trachcobronchial anomaly; TM = tracheomalacia; TOF = tetralogy of Fallot; TVD = tricuspid value dysplasia; UH = ulnar hypoplasia; UTI = urinary tract infection; VSD = ventricular septal defect.

or corneal opacity (n = 7, 29%), microphthalmia (n = 3, 13%), congenital glaucoma (n = 2, 8%), and iris coloboma (n = 2, 8%). Seventeen (71%) children had limb defects, including polydactyly (n = 15, 63%). Six (25%) children had urinary tract infection. One (Individual 6) child developed neuroblastoma at 4 months.

3.3 | Treatment

Data of treatment are shown in Table 2. Mechanical ventilation was performed in 21 (88%) children, including intermittent mandatory ventilation (n = 19, 79%) and nasal continuous positive airway pressure (n = 2, 8%). Among those receiving intermittent mandatory ventilation, 7 (37%) were extubated and 12 (63%) underwent tracheostomy. Fourteen (58%) children had pharmacological treatment for cardiac diseases, including diuretics (n = 13, 54%), dopamine with or without dobutamine pressors (n = 3, 13%), and prostaglandin E1 (n = 3, 13%). A total of 43 surgical procedures were performed on 17 (71%) children, including tracheostomy (n = 14, 58%), gastrostomy (n = 7, 29%), polydactyly repair (n = 6, 25%), cheiloplasty (n = 4, 17%), omphalocele repair (n = 3, 13%), and plication for diaphragmatic eventration (n = 2, 8%) (Shibuya et al., 2018). Three (13%) children used a hearing aid.

3.4 | Feeding and growth

Twenty-one (88%) children were fed enterally. Seven (29%) children were fed orally. Fourteen (58%) children were given total parenteral nutrition. Enteral tubes to the duodenum were used in eight (33%) children with gastroesophageal reflux. Blended foods were provided through gastrostomy to five (21%) children. One (Individual 5) child had feeding therapy for oral suckling from the neonatal period. Another (Individual 17) child had assessment for oral suckling at 30 days old, and showed a mild and irregular suckling reflex, delay of the swallowing reflex, and a high risk of aspiration. He had feeding therapy for suckling and swallowing using a swab with milk. He started bottle feeding at 2 months old, completed it at 7 months, and started to have baby food at 10 months. He drank milk and had blended foods at 2 years old. One (Individual 19) child had feeding therapy for thickened liquid at 3 years and 2 months old. One (Individual 20) child had nonnutritive oral sensorimotor stimulation for oral hypersensitivity and another (Individual 21) had liquid orally using a syringe and had blended foods. One (Individual 23) child had soft foods orally at 5 years old. Four (Individuals 17, 19, 20, and 21) children had assessment by a multidisciplinary dysphagia team. They showed an abnormal oral sensation, uncoordinated tongue movement, incoordination of oral and pharyngeal phases, and discoordination between sucking and swallowing, and had inappropriate sizes and forms of food and a presumed risk of aspiration. Growth curves were constructed for five boys and two girls (Figure 1). Only one girl (Individual 16) showed growth disturbance.

3.5 | Development

Children with long-term survival showed slow, but constant motor and social development in relationship with their families. At 1 year and 8 months, Individual 17 raised his head, rolled over, smiled, babbled, played with a toy, and was fed with a spoon (Figure 2a). His developmental quotient for posture and motion was 19 (developmental age, 3.8 months). At 3 years and 3 months, Individual 19 sat with support, moved the limbs, showed sucking movements, and gazed at parents and caregivers (Figure 2b). At 3 years and 7 months, Individual 20 rolled over, babbled, smiled, and gazed at parents and colorful toys (Figure 2c). At 6 years and 1 month, Individual 21 sat with support, rolled over, moved back and forth with her back on the floor, and moved with a walker (Figure 2d). At 8 years and 2 months, Individual 22 sat with support, rolled over, moved with a walker, and smiled when spoken to by others (Figure 2e). His developmental quotient was 17 at 2 years and 2 months (developmental age, 4.1 months), 13 at 3 years and 5 months (developmental age, 5.3 months), and 11 at 4 years and 5 months (developmental age, 5.8 months). At 8 years and 10 months, Individual 23 sat with support, rolled over, and moved with a walker (Figure 2f). Individual 24 died at 10 years and 11 months, had rolled over, sat with support, and enjoyed playing with toys. No expressive language was noted in this series.

3.6 | Prognosis

Prognosis of the children is shown in Table 2. Eleven (46%) children were discharged home. The median hospital stay of the first admission among the 10 children, except for Individual 24 (data not available), was 326 days (range, 68–395 days). The survival rates at 1 week, 1 month, 1 year, 3 years, 5 years, and 10 years old were 100%, 95.8%, 54.1%, 25.0%, 16.7%, and 4.2%, respectively. The median survival time was 451 days for both sexes (range, 22–3987 days), 522 days for boys (range, 154–3600 days), and 310 days for girls (range, 22–3987 days).

The most frequent underlying factors associated with death, among 16 children who had died at the time of this study, were congenital heart defects and heart failure (n = 10, 63%), followed by infection (sepsis or pneumonia) (n = 5, 31%), and pulmonary hypertension (n = 3, 19%). The most frequent final mode of death was heart failure (n = 8, 50%). One (Individual 6) child had neuroblastoma at 4 months old and died at 6 months. One (Individual 13) suffered from an acute gastrointestinal hemorrhage, and finally died of arrhythmia. One (Individual 17) child, who had an atrial septal defect and a ventricular septal defect without heart failure, developed sudden cardiac arrest at home at 2 years and 7 months old, possibly associated with an infection.

4 | DISCUSSION

This is the first detailed and comprehensive institution-based study on the natural history of T13, in which all the patients were managed under the principle of providing standard intensive neonatal and pediatric treatment without cardiac surgery. Detailed clinical evaluation was made in all of the admitted children, even in those with a short survival. Therefore, the frequency of congenital heart defects (92%) in the current study is thought to be the most accurate compared with previous institution-based or population-based studies, which showed a frequency ranging from 34.8% to 100% (Baty, Blackburn, & Carey,

TABLE 2 Medical interventions, feeding, prognosis and cause of death of patients with T13

	Medical intervention											*Prognosis*			
	Respiratory care							*Feeding*			*Others*			*Cause of death*	
Case	Mechanical ventilation	Mode of ventilation	Weaning	Tracheostomy	Cardiovascular	Anticonvulsant	Surgical intervention	Enteral feeding	D tube	Oral feeding		Discharge (days)	Survival time (days)	Underlying factor	Final mode of death
1	+	IMV			–		–	+		+		–	22	SE	SE
2	+	CPAP	+		D, DO		–	+				–	93	CHD	HF
3	+	IMV	+		–		Repair of omphalocele	+				–	122	CHD, PH, BR	HF, RF
4	+	IMV			D, PGE1		Repair of omphalocele, diaphragma plication, TS					–	154	CHD	DIC, MOF
5	+	IMV		+	D		TS, repair of polydactyly	+	+	+		–	171	CHD	HF
6	–				–		–	+				–	189	NB	NB
7	+	IMV			D		–	+			Hot's plate	–	227	CHD	HF
8	+	IMV		+	DO		TS	+	+			–	232	CHD, PH	PHE, HF
9	+	IMV		+	D		TS	+	+			–	310	CHD	HF
10	+	IMV			D, PGE1			+				–	331	CHD, HF, SE	HF
11		IMV			D, PGEI		Ileostomy	+	+.			–	340	CHD, HF, SE	DIC, BH
12	+	IMV	+	+	–		TS, repair of polydactyly	+				–	444	Aspiration PN	RF
13	+	IMV			D, PGEI		–					–	458	GH	AR
14	–		+[a]	+	D, DO		TS, chelioplasty					+(395)	522	CHD, PH	PHE, HF
15	+	IMV		+		VPA	Repair of omphalocele, TS, GS, diaphragma plication	+	+			+(361)	792 (live)		
16	+	IMV				LEV, PB	TS	+	+			+(375)	850 (live)		
17	+	CPAP				–		+		+		+(68)	1008	Infection	SCA
18	+	IMV	+	+		PB	Repair of polydactyly, TS, GS, orchiopexy	+				+(288)	1086 (live)		
19	+	IMV	+	+	D	VPA	TS,GS,chilioplast.v, Skin tumor excision	+		+	HA	+(81)	1554 (live)		
20	+	IMV		+	D	LEV,VPA	TS, GS	+	+	+	HA	+(390)	1659 (live)		
21	+	IMV		+	D	PB, VPA ZNS	TS, repair of polydactyly, GS, hepatic portenterostomy, cheilioplasty, cataract surgery, palatoplasty, tympanostomy	+		+	HA	+(315)	2586 (live)		
22	+	IMV		+	D, ACEI, BE	LEV,VPA ZNS	TS, GS, Ladd's operation	+				+(283)	3359 (live)		
23	+	IMV	+	+	D	VPA	TS, GS, repair of polydactyly	+	+	+		+(337)	3600 (live)		
24	–					PB	Repair of polydactyly, chelioplasty	+				+	3987	PN	RF

ACEI = angiotensin converting enzyme inhibitor; AR = arrhythmia; BE = beraprost natrium; BH = brain hemorrhage; BR = bronchitis; CPAP = continuous positive airway pressure; CHD = congenital heart defect; D = diuretics; DIC = disseminated intravascular coagulation; DO = dopamine with or without dopamine pressors; D tube = duodenal tube; GH = gastrointestinal hemorrhage; GS = gastrostomy; HA = hearing aid; HF = heart failure; IMV = intermittent mandatory ventilation; LEV = levetiracetam; MOF = multiple organ failure; NB = neuroblastoma; PB = phenobarbital; PGE1 = prostaglandin EI; SCA = sudden cardiac arrest; PH = pulmonary hypertension; PHE = pulmonary hemorrhage; PN = pneumonia; RF = respiratory failure; SE = sepsis; TS = tracheostomy; VPA = valproate; ZNS = zonisamide.

[a] Individual 14 needed an airway tube.

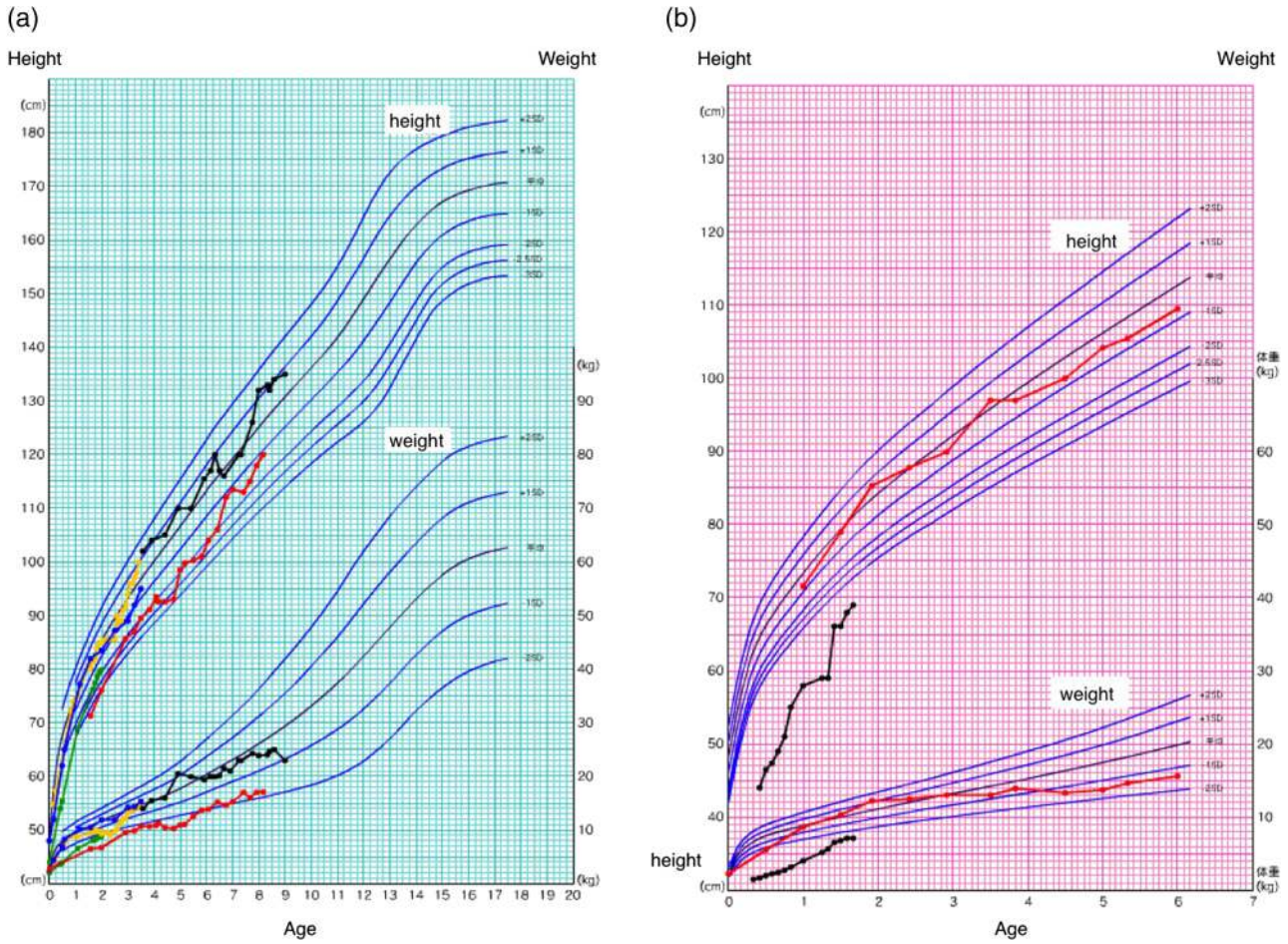

FIGURE 1 Growth curves for children with T13. (a) Boys (black, Individual 23; red, Individual 22; yellow, Individual 20; blue, Individual 19; green, Individual 17). (b) Girls (red, Individual 21; black, Individual 16)

1994; Baty, Jorde, Blackburn, & Carey, 1994; Hodes, Cole, Palmer, & Reed, 1978; Lin et al., 2007; Maeda et al., 2011; Moreman, Fryns, van der Steen, Kleczkowska, & Lauweryns, 1988; Petry et al., 2013; Polli et al., 2014; Rasmussen et al., 2003; Taylor, 1968; Wyllie et al., 1994). This wide range might have been related to the variable frequency and accuracy of cardiac evaluation among these series based on variable intensiveness of management in each child, especially in population-based studies. Detailed cardiac evaluation in the current series detected, for the first time, several defects, including aortopulmonary window and pulmonary-ductus-descending aorta-trunk. Furthermore, our careful multisystem observation showed the frequency of laryngomalacia and/or tracheomalacia (42%) and identified biliary system abnormalities, eosinophilic enteritis, and neuroblastoma.

We found a markedly longer survival (1-year survival rate, 54%; median survival time, 451 days) compared with previous series in which variable therapeutic approaches that were probably skewed to a palliative approach were adopted (1-year survival rate, 0%–37.5%; median survival time, 2.5–44.5 days) (Supporting Information Table 1) (Brewer, Holloway, Stone, Carothers, & FitzPatrick, 2002; Goldstein & Nielsen, 1988; Lin et al., 2007; Meyer et al., 2016; Polli et al., 2014; Rasmussen et al., 2003; Tsukada, Imataka, Suzumura, & Arisaka, 2012). Therefore, the current study provided evidence that standard intensive neonatal and pediatric management without cardiac surgery improved survival of children with T13 for the first time, which was demonstrated in those with T18 from our previous series (Kosho et al., 2006). Longer survival in this series might have also be attributable to longer hospital stay (the median 326 days in discharged cases) through higher level of care from nursing staff and physicians. Recently, a large-scale, retrospective study from Ontario showed that the 1-year survival was 19.8% and the median survival time was 12.5 days (Nelson, Rosella, Mahant, & Guttmann, 2016). This previous study recruited 41 children who underwent surgeries, ranging from myringotomy to complex heart defect repair. The median age at the first surgery was 92 days and the 1-year survival after the first surgery was 70.7%. However, the authors noted that the study did not determine the efficacy of surgical procedures on survival because of the heterogeneity of the cohort and procedures (Nelson et al., 2016).

In the current study, there was no significant difference in survival of boys and girls with T13 (Figure 3a). There were also no significant differences in birth weight, gestational age, the Apgar score at 1 and 5 min, and presence or absence of complex congenital heart defects, tracheomalacia/laryngomalacia, and holoprosencephaly between children who survived for 1 year and those who did not (Supporting Information Table 2). A lack of factors related to longer survival in this study suggests that predicting a newborn's survival at birth or even in the prenatal period may not be possible. Interestingly, survival of children with T13 in this series was significantly longer than that with T18 in our previous series (Kosho et al., 2006) (Supporting Information

FIGURE 2 Clinical photographs. (a) Individual 17 at age 1 year and 8 months. (b) Individual 19 at 2 years and 10 months. (c) Individual 20 at 4 years and 7 months. (d) Individual 21 at 6 years and 9 months. (e) Individual 22 at 7 years and 9 months. (f) Individual 23 at 8 years and 0 months

Table 3). The median survival time was 451 days in those with T13 and 145 days in those with T18 (Figure 3b). Previous large-scale, population-based studies showed that survival of children with both conditions was not significantly different (Rasmussen et al., 2003; Nelson et al., 2016).

The major underlying factor associated with death in our study was congenital heart defects and heart failure (63%) and the major final mode of death was heart failure (50%). In our previous study on children with T18 who were treated under standard neonatal management without cardiac surgery, the major underlying factor associated with death was congenital heart defects and heart failure (96%), followed by pulmonary hypertension (78%) (Kosho et al., 2006). In addition, the major final mode of death was sudden cardiac or cardiopulmonary arrest (26%) and possible progressive pulmonary hypertension-related events (26%). Therefore, cardiac surgery could contribute to longer survival of children with T13, as well as of those

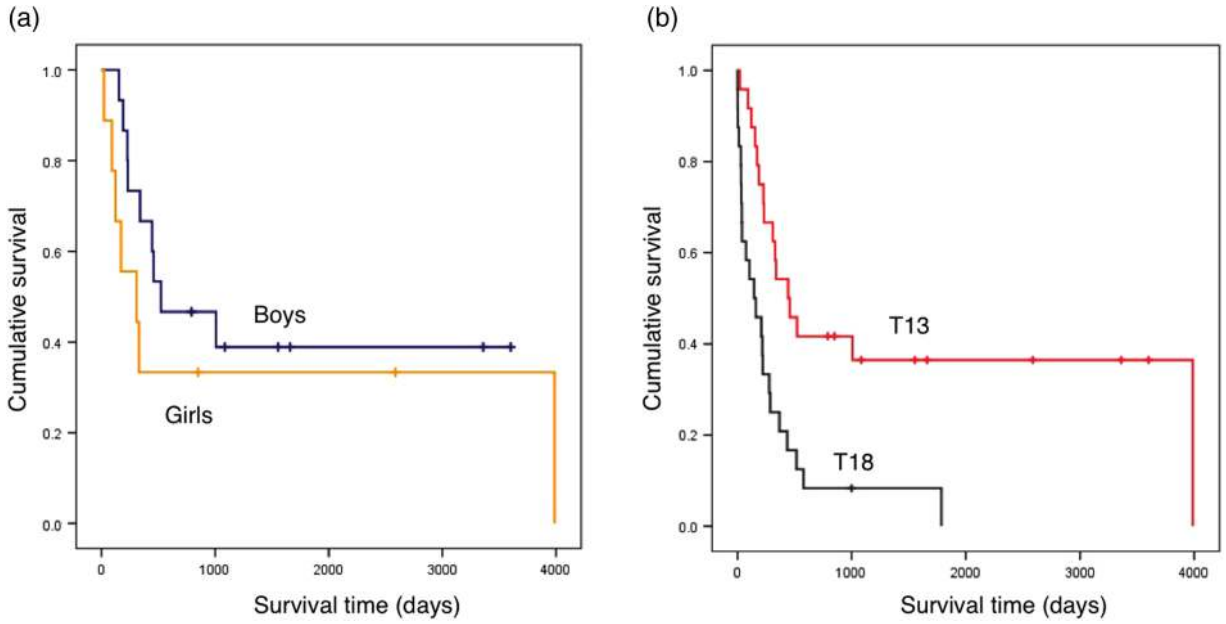

FIGURE 3 Survival curves. (a) Kaplan–Meier survival curve of children with T13 (blue, boys; yellow; girls). (b) Kaplan–Meier survival curve of children with T13 (red) or T18 (black) [Color figure can be viewed at wileyonlinelibrary.com]

with T18. However, considering the difference in the rate of the major underlying factor associated with death as congenital heart defects and heart failure (63% for T13 vs. 96% for T18), the effect of cardiac problems (congenital heart defects, heart failure, and also pulmonary hypertension) on death directly or indirectly might be weaker in children with T13 than in those with T18.

The current series showed that long-term survivors appeared to have extremely slow, but continued progressive motor development. Some long-term survivors rolled over at approximately 4 years old and moved with walkers at 6 years, but could not sit unassisted. These observations appear to be slower than those described in a previous support group-based study (mean age of achieving of rolling over, 11.2 months; that of moving with walkers, 32.5 months; that of sitting unassisted, 31.0 months) (Baty, Blackburn, et al., 1994; Baty, Jorde, et al., 1994). This discrepancy between studies might be attributable to the difference in clinical severity. More severely affected children could have survived and been included in the current study through intensive treatment than in previous series (Baty, Blackburn, et al., 1994; Baty, Jorde, et al., 1994). Long-term survivors in the current series also appeared to have subtle, but continued progressive psychosocial achievement with emotional maturation. However, more systematic approach would be required for evaluating such subtle psychosocial development in children with severe intellectual disability, as shown in a study by Braddock et al. (2012) demonstrating communicative ability of individuals with T18 or T13 through caregivers' records and videotaped responses of those with T18 or T13 and in another study by Liang et al. (2015) describing children's potential communication acts, words, spontaneous gesture, and augmentative and alternative communication.

Management of children with T13 has changed, based on the addition and/or revision of evidence in natural history and medical intervention, as well as transitions in patient–physician relationships and in the value and purposes of medical intervention (Carey, 2010). Efficacy of cardiac surgery has been shown in several previous studies (Graham et al., 2004; Kaneko et al., 2008; Maeda et al., 2011). The efficacy of intensive neonatal and pediatric management without cardiac surgery was also found in the current study. Slow, but constant, psychomotor development in long-term survivors with T13 has been described in a support group-based study (Baty, Blackburn, et al., 1994; Baty, Jorde, et al., 1994), and was also found in the current series. Furthermore, in another support group-based study (Janvier, Farlow, & Wilfond, 2012), most of the parents described that their children with T13 were happy and its effect on their lives was positive. In view of this evidence, intensive neonatal and pediatric management might be a reasonable choice for parents of these children. Authors of a recent review stressed the importance of carefully considering available data on the current status of practices related to care from palliation to intensive interventions (McCaffrey, 2016). This review also suggested that physicians should rise above their personal prejudices and listen to the families imploring them to consider their opinions regarding the value of the life of a child with T13, as well as T18 (Janvier et al., 2012). Authors from another review proposed shared decision-making in management of children with T13 or T18 (Andrews et al., 2016). This robust process aims at collaborative development of goals of care, actively engaging the expertise and perspectives of both parents and clinicians. Care pathways should be evidence-based, condition-specific, stepwise approaches that are designed to improve standardization of care, quality, and outcome (Andrews et al., 2016).

5 | CONCLUSION

Intensive neonatal and pediatric treatment without cardiac surgery in children with T13 would be efficient for survival regardless of the severity of heart diseases, and consequently psychomotor development. Cardiac surgery could contribute to longer survival considering the high rate of heart-related death in this series. Our data will be helpful for parents of children or fetuses with T13, as well as all medical, educational, and social support staffs participating in the comprehensive multidisciplinary care of them.

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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