

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

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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. © 2013 Wiley Periodicals, Inc.

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

INTRODUCTION

Trisomy 18 is the third most common autosomal aberration syndrome in liveborn infants after trisomy 21 and 22q11.2 deletion

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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

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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

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

(Continued)

TABLE 1. (Continued)

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

(Continued)

TABLE I. (Continued)

| Case number | Prenatal ultrasonographic findings/karyotyping | | | Pregnancy and delivery | | Complications | | | | Management | | | Outcomes | | | | | | |
|-------------|--|-----|--------------|------------------------|-----------|----------------------------|----------------|----------|-------|------------|---------------------|----------|----------|----------------|------------------------|--------------|-------------------------------|-----------------------|----------------|
| | Survival (days) | Sex | Survival (s) | Gestational weeks/day | 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 of death |
| 63 | 10/4L | F | 1456 | 35/2 | + | PDA | LH, At, LM | Sy | — | — | — | GT(11w) | In | Di, Ph, Ch, VD | IMV | NO | — | Many | — |
| 64 | 12/4L | F | 2560 | 41/1 | — | VSD, CoA | DE | Sy | — | — | — | — | — | — | — | FO | +(4w) | Many | — |
| 65 | 26/4L | M | 2460 | — | — | — | — | — | — | — | — | — | — | — | — | FO | + | Many | — |

Blank, not described; +, present; —, absent; *, temporary return to home; AA, anal atresia; Aa, anti-allergic agent; Ab, antibiotics; Ac, anticonvulsant; Ap, apnea; AS, aortic stenosis; ASA, acetyl salicylic 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, cardiotoxic 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, exsiccator; 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; HM, 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; PHe, pulmonary hypertension; PH, prolapsed hindbrain; PH, prostaglandin; PH, pulmonary stenosis; 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; Si, at sleep; SoB, sodium bicarbonate; Sp, spontaneous recovery; SRA, serotonin receptor agonist; St, recovery by manual stimulation; SUP, sinus urogenitalis persistence; Sy, syndactyly; Sz, seizure; TE, talipes equinovarus; TEF, tracheoesophageal fistula; Th, L-thyroxine; TOf, tetralogy of Fallot; TS, tracheal stenosis; Ub, ubidecarenone; URi, upper respiratory tract infection; UT, undescended testis; V, vitamin; VD, 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 was 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 cesareans, 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/ventration) 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 epilepticus, 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 cardiotoxic 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

| Characteristics | Survival <1y | Survival >1y | P-value |
|--|------------------|------------------|--------------|
| Female | 60 (27/45) | 83 (15/18) | 0.076 |
| Mean gestational week at birth (\pm SD) | 38.25 \pm 3.38 | 40.43 \pm 2.01 | 0.011 |
| Mean birth weight (g) (\pm SD) | 1814 \pm 405 | 2180 \pm 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 \pm 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 mosaicism.

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 non-profit 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.

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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.