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Original Article

National survey of prevalence and prognosis of thanatophoric dysplasia in Japan

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Abstract ***Background*:** Thanatophoric dysplasia (TD) is a rare congenital disease of the skeletal system, with an incidence of 1.68–8.3 per 100 000 births, but statistical data on the estimated number of TD patients across Japan are not available. The aim of this study was therefore to investigate the prevalence and prognosis of TD in Japan.

***Methods*:** A nationwide primary questionnaire survey was conducted.

***Results*:** A total of 127 obstetric, 186 pediatric, and 115 orthopedic facilities provided responses. Excluding duplications, we identified 73 patients with TD. Of the 73 cases, 15 were abortions, four were stillbirths, 51 were live births, and three had unknown details. Of the 51 live newborns, 27 died ≤7 days after birth, with an early neonatal mortality rate of 56%. Of the 24 newborns who survived the early neonatal period, 16 survived for ≥1 year. All of the 24 newborns received respiratory management and survived during the early neonatal period. Of the 51 live newborns, 25 did not receive respiratory management and died ≤2 days after birth.

***Conclusions*:** The prevalence of TD in Japan is estimated to be at 1.1 (95%CI: 0.84–1.37) per 100 000 births, but the actual incidence is expected to be higher. To our knowledge, we have confirmed for the first time that newborns with TD may not always die during the early neonatal period but can survive the early neonatal period with appropriate respiratory management. Therefore, the term "thanatophoric dysplasia" does not accurately reflect the nature of the disease.

Key words epidemiology, newborn, osteochondrodysplasia, survey, thanatophoric dysplasia.

Thanatophoric dysplasia (TD) is the most common form of lethal neonatal skeletal dysplasia.[1] TD is caused by mutations of the gene encoding fibroblast growth factor receptor 3 (FGFR3)[2] and is characterized by marked shortening of the limbs, narrow thorax, macrocephaly with frontal bossing, and a relatively normal trunk length. Infants with TD usually die soon after birth without intensive medical intervention,[2] forming the basis of the disease name (*thanatophorus* in Greek, which means "death bringing" or "death bearing").

The prevalence of TD is 2.1–3 per 100 000 live births (1 per 33 330–1 per 47 620 live births) in the USA,[3] 5 per 100 000 live births in Latin America,[4] and 2.4 per 100 000 live births in West Scotland.[5] While there have been several isolated case reports of TD in Japan,[6–8] a 1999 study reported a comparatively low TD prevalence rate of 0.29 per 100 000 births in Japan.[9] That study, however, was based on surveys performed primarily at pediatric facilities and likely excluded stillbirths involving TD that would be captured by surveying obstetric facilities. Furthermore, prenatal diagnosis on genetic examination for TD was not commonly performed prior to 1999 and may have contributed to the underreporting of TD prevalence.

Traditionally, postnatal diagnosis of TD was based on radiographic skeletal abnormalities in the newborn. Patients with TD have been classified into two types (TD1 and TD2) based on the presence or absence of a "clover-leaf" skull or presence of curved/straight femurs. The more common TD1 is characterized by curved femurs ("telephone receiver appearance") and usually does not present with a clover-leaf skull. In contrast, TD2 patients have relatively straight femurs and a clover-leaf skull.[1,2] Molecular analysis of *FGFR3* is also now being used to confirm TD diagnosis in newborns. Owing to the high risk of postnatal mortality, prenatal diagnosis of TD is commonly performed using ultrasonography, 3-D helical computed tomography (3-D CT), or mutation analysis of the

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causative gene *FGFR3*.[8,10,11] In light of these advancements in genetic diagnosis and medical imaging technology, we speculate that a new survey that includes obstetric, pediatric, and orthopedic facilities would provide a more accurate estimation of TD prevalence.

Furthermore, the Japanese term for TD, being a direct translation from the Greek term *thanatophoric*, highlights the lethal aspect of the condition and is a cause of great concern, pessimism, and stigma among the family of patients with TD. Although TD is conventionally viewed to be lethal in the early neonatal period, several studies have reported longer survival in patients with TD.[12–14] To date, no survey on the postnatal course of TD has been reported. Therefore, a second objective of this study was to investigate the prognosis of TD after birth and to examine whether TD is in fact lethal in the early neonatal period.

Methods

The study was performed within the framework of scientific research for the diagnosis and prognosis of TD according to the Ministry of Health, Labour and Welfare of Japan. A questionnaire was mailed to university hospitals, general perinatal medical centers, regional perinatal medical centers, and children's medical centers, which were routinely involved in the diagnosis and treatment of TD. The questionnaire was addressed to 381 obstetric, 394 pediatric, and 381 orthopedic facilities.

The questionnaire inquired about the number of patients with TD managed at each department between April 2005 and September 2010. Detailed information on the sex, gestational age, methods of diagnosis, clinical findings, complications, respiratory treatment methods, physical findings, and survival time was also requested. Considering the issue of pessimism surrounding the Japanese term for TD, we included a question about the view of the respondents regarding the validity of the Japanese term and the reason for each view.

Statistical analysis

Kaplan–Meier survival analysis was performed to evaluate the effect of respiratory management on patients with TD. Statistical analysis was performed using JMP (SAS Institute Japan, Minato-ku, Tokyo, Japan).

This study was approved by the Medical Ethics Committee of Kyoto University.

Results

Responses were obtained from 127 obstetric facilities (33.2%), 186 pediatric facilities (47.2%), and 115 orthopedic facilities (30.2%). A total of 85 patients with TD were reported: 53 from obstetric facilities, 30 from pediatric facilities, and two from orthopedic facilities. Detailed data were not available for five patients from pediatric facilities, and overlapping data were obtained from multiple facilities or departments for seven patients. These 12 patients were excluded, and analysis was performed using the data obtained from 73 patients (Fig. 1).

Of the patients, 27 were boys and 38 were girls; sex was not known in eight patients. TD1 was present in 43 patients; and TD2, in eight; the type of TD was unknown in 22 patients. Eleven patients underwent *FGFR3* genetic testing, of whom eight had TD1, with three having a cDNA 742 C>T mutation (Arg248Cys mutation in amino acids), three having a 1118 A>G mutation (Tyr373Cys in amino acids), and two having unknown/unavailable mutation data. One patient had TD2 and carried a cDNA 1948 A>G mutation (Lys650Glu mutation in amino acids). Two patients with unknown TD type did not have a mutation in *FGFR3*.

Thanatophoric dysplasia was diagnosed at a gestational age of <22 weeks in 19 patients on the basis of diagnostic imaging. Intrauterine diagnosis after the gestational age of 22 weeks was made in 43 patients. The condition was diagnosed after birth in 11 patients. Of the 19 patients diagnosed at gestational age <22 weeks, 15 underwent induced abortion. The outcome of pregnancy in the other 58 patients was stillbirth in four, live birth in 51, and unknown in three. Of the 31 live newborns with available information on the manner of delivery, 12 were delivered by cesarean section for reasons of cephalopelvic disproportion (CPD) in six cases, breech presentation in five, and mother's strong desire for cesarean delivery because of anxiety about the sick fetus in one.

The clinical findings from 51 live newborns with available data are presented in Figure 2. Short limbs were noted in all patients; narrow thorax, in 90%; respiratory insufficiency, in 84%; and bowed femurs in 78%. The overall survival data of 51 live newborns are presented in Figure 3, Table 1. Twenty-four patients died on the first day, three died on the second day, and the remaining 24 live newborns survived past the early neonatal period. Thus, the early neonatal death rate was 56% (31/55, including the four stillbirths). The cause of death in the 33 patients, regardless of the time of death, was respiratory failure in 23 patients, heart failure in two, ileus/acute respiratory distress in one, and unknown in seven. All seven patients in whom the cause of death was unknown died ≤2 days after birth, and six were reported to have a narrow thorax and respiratory insufficiency.

The postnatal respiratory management and survival rates are summarized as follows: Of the 51 live newborns, 24 received respiratory management and 16 (66.6%) survived for ≥1 year. Of these 16 survivors, seven underwent tracheotomy and six underwent tracheal intubation, while detailed information about the remaining six survivors was unavailable. Biphasic positive airway pressure, directional positive airway pressure, synchronized intermittent mandatory ventilation, or high-frequency oscillation was selected as the mode of mechanical ventilation, depending on the individual patient condition. No attempt at resuscitation was made in the case of 25 patients after birth, all of whom died ≤2 days after birth. Among the live newborns, detailed information on respiratory management was unavailable in two patients, and both died ≤2 days after birth.

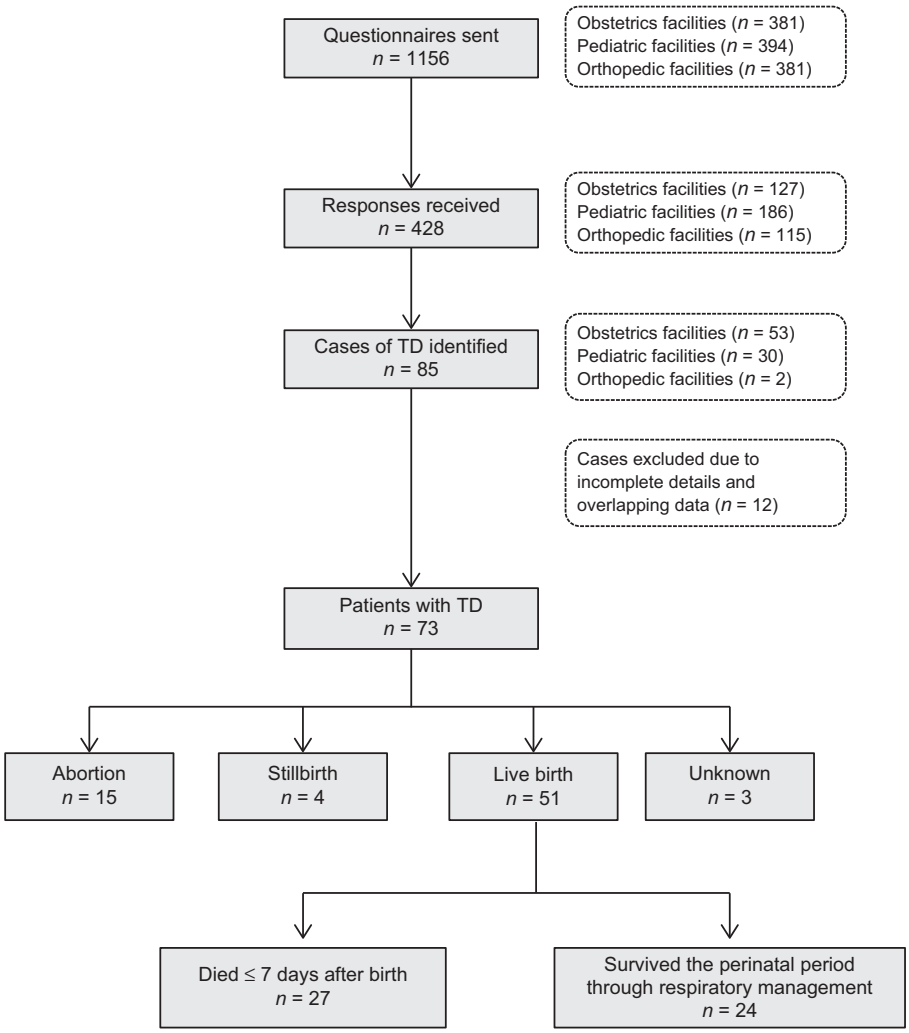

Fig. 1 Schematic diagram of subject selection. TD, thanatophoric dysplasia.

Of the 17 survivors confirmed at the time of the investigation, nine were receiving care as inpatients, and five were receiving care at home; details about the remaining three were unknown after referral to other facilities.

Discussion

According to the present survey, 73 patients were diagnosed with TD during the study period, between April 2005 and September 2010. Of these patients, 51 were live newborns (9.27 births/year), which was greater than the number (16 patients, 3.20 births/year) reported previously in Japan for the period January 1995–December 1999.[9]

Assuming an estimated total of 6 million births in Japan during the survey period,[15] live births with TD during this period (excluding seven patients who were not born during the survey period) yielded a rate of 0.73 TD cases per 100 000 births. Combining the 44 live births, 15 induced abortions, four stillbirths, and three cases with unknown details, for a total of 66 cases, the TD prevalence during the second trimester of pregnancy (when short limbs are detectable on diagnostic imaging) was estimated to be 1.1 (66/60; 95%CI: 0.83–1.37 per 100 000 births).

This estimate is approximately equal to that reported in a recent regional survey in the USA (2.1–3 per 100 000)[3] and is consistent with the conventionally reported TD prevalence (1.68–4.0 per 100 000 births), thereby suggesting the lack of ethnic difference in TD prevalence.[16,17] It should, however, be noted that the response recollection rate was <50% in this survey, and some patients with TD may have been delivered, in the case of women who decided to undergo induced abortion after detection of a fetal anomaly (severely short limbs) during the first trimester of pregnancy, particularly at facilities not included in this survey. A recent study suggested that the incidence is higher (4.7–8.3 per 100 000 births).[18,19,20,21] To our knowledge, no national range or estimate has been established for the incidence of TD in Japan. If one considers the possible data from the non-response facilities, the actual incidence of TD in Japan would be higher than that estimated in the present study (0.83–1.37 per 100 000 births). Unfortunately,

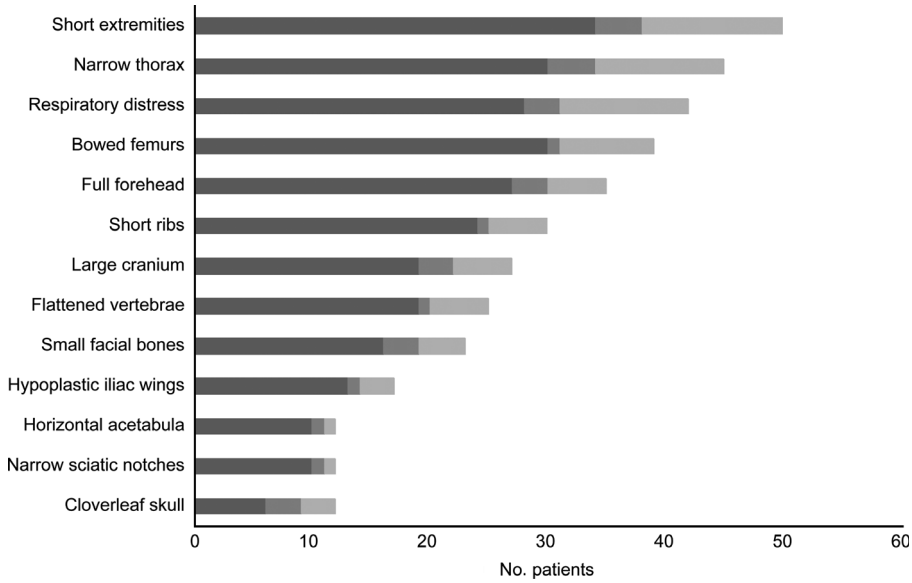

Fig. 2 Distribution of clinical findings in live newborns with thanatophoric dysplasia (TD) according to type (n = 51): (■), type 1; (■), type 2; (■), unknown. Respiratory insufficiency is attributable to the narrow thorax. Bowed femurs are attributable to short limbs. Thus, short limbs and narrow thorax were identified as the common clinical features of patients with thanatophoric dysplasia.

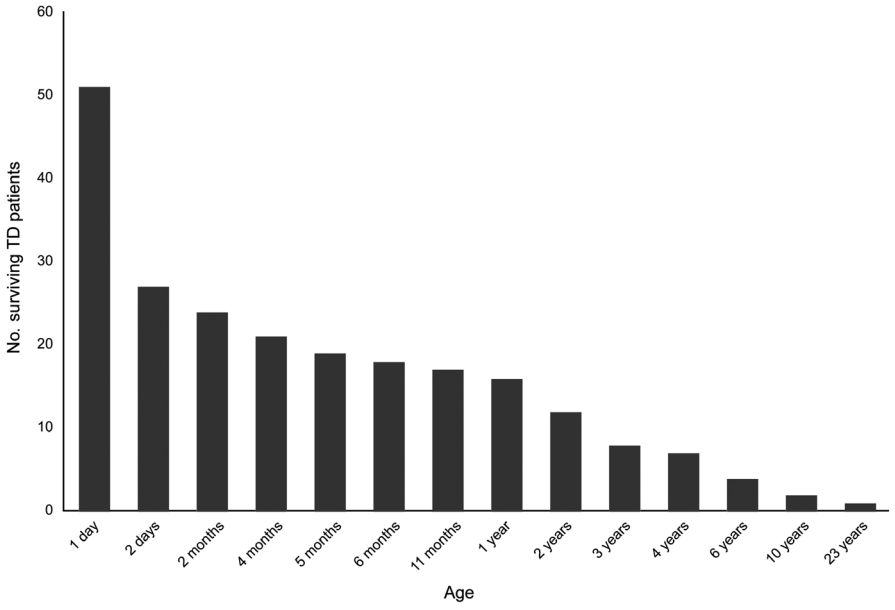

Fig. 3 Distribution of surviving thanatophoric dysplasia (TD) subjects (n = 51) according to age.

owing to the limitations of the present low response rate, the uncontrollable factor of induced abortion at an early stage of pregnancy, and operational limitations of patient transfer to a specialized medical facility, we could not perform a thorough statistical analysis, because it may lead to a skewed representation for the incidence of TD in Japan.

Thanatophoric dysplasia has conventionally been regarded to be fatal during the early neonatal period, and respiratory insufficiency due to narrow thorax has been considered a direct cause of early neonatal death in patients with TD.[22] In the present survey, 51 live newborns had TD, and 16 of the 24 patients who received respiratory care survived for ≥1 year, while all 25 patients who did not receive respiratory management after birth died in ≤2 days. Therefore, respiratory management appears to be necessary and indispensable for prolonging the survival of newborns with TD.

The long-term survival of newborns with TD has been reported in several isolated reports. Stensvold *et al*. reported a 169 day survivor, and Tonoki reported a 212 day survivor, both of whom died from respiratory insufficiency.[19,22] McDonald *et al*. reported the cases of 2 children alive at age 4.0 and 4.75 years, respectively, stating that respiratory

Table 1 Thanatophoric dysplasia (n = 51): Kaplan–Meier survival table

Age	n	Dead	Censored	Conditional probability		Survival standard deviation
				of survival	of death	
1 day	51	24	0	0.5294	0.4706	0.0699
2 days	27	3	0	0.4706	0.5294	0.0699
3 months	24	3	0	0.4118	0.5882	0.0689
4 months	21	1	1	0.3922	0.6078	0.0684
5 months	19	0	1	0.3922	0.6078	0.0684
6 months	18	1	0	0.3704	0.6296	0.0680
11 months	17	0	1	0.3704	0.6296	0.0680
1 year	16	0	4	0.3704	0.6296	0.0680
2 years	12	0	4	0.3704	0.6296	0.0680
3 years	8	0	1	0.3704	0.6296	0.0680
4 years	7	1	2	0.3175	0.6825	0.0761
6 years	4	0	2	0.3175	0.6825	0.0761
10 years	2	0	1	0.3175	0.6825	0.0761
23 years	1	0	1	0.3175	0.6825	0.0761

management was important in both patients.[18] Nikkei et al reported one of the patient in ref.[18] was still living and 28 years of age.[14] In addition, the cases of 9- and 23-year-old patients with TD in whom the condition was definitively diagnosed on genetic testing and who received respiratory management after diagnosis, have been reported.[12,13] These findings support the need for respiratory management for long-term survival of patients with TD. The present results provide additional evidence for the importance of respiratory management by showing that all patients who did not receive any respiratory management after birth died in ≤2 days. In contrast, 24 of the 51 live newborns who received respiratory management survived the early neonatal period, and 16 (66.6%) of the 24 patients survived for ≥1 year. TD is not lethal under adequate respiratory support. These amazing results highlight the necessity of revising the Japanese term for TD, which emphasizes the inevitably fatal nature of the disease.

Thanatophoric dysplasia was diagnosed on the basis of postnatal radiographs in all cases of living patients, but we could not perform postnatal radiography in the cases of abortion. Furthermore, only a few cases could be diagnosed phenotypically without a requirement for radiography. Nonetheless, because TD is attributable to mutation of *FGFR3* and because the mutation is concentrated at several sites in the gene, genetic diagnosis is also greatly useful.[11] In the present survey, seven patients underwent genetic examination that identified an *FGFR3* mutation: three TD1 patients with a cDNA 742C>T mutation, three TD1 patients with a cDNA 1984A>G mutation, and one TD2 patient with a cDNA 1948A/G mutation. All these mutations were previously known and were concentrated at previously known specific sites.[23] Information on subtype was unavailable in 22 of the 73 patients in this survey, but two of the 22 patients underwent *FGFR3* analysis that showed no mutation. The number of patients who underwent genetic analysis was too small to allow analysis of the differences in postnatal course depending on gene type. This is one of the limitations of the present study, wherein we could not diagnose all cases on postnatal radiography and *FGFR3* mutation.

The inherent limitations of retrospective studies also exist in this study. Given that no TD registration system covers all births in Japan, we mailed a questionnaire to individual facilities. Thus, this survey cannot be considered to cover all cases of TD, in view of the partial response rate and the patients lost before birth. Future studies will aim to conduct a more detailed and prospective evaluation of the prognosis of TD, including analysis of the growth and development of survivors, to understand the natural history of TD in greater detail.

The preliminary data of this study were used as reference for developing a new system of Intractable Diseases by Ministry of Health and Welfare of Japan and led to the development of the diagnostic criteria for TD in the System of Designated Intractable Diseases of Japan. Furthermore, the translation of TD in Japanese was revised from "lethal bone dysplasia" to "thanatophoric dysplasia" in Japanese, this avoids the ambiguity and is not offensive or distressing to patients and their families.[24]

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Disclosure

The authors declare no conflict of interest.

Author contributions

H.S. designed the study and wrote the manuscript; K.O. performed the study, obtained general results, and wrote the draft in Japanese; M.U. helped in the conduct of the study; G.N. provided conceptual advice on skeletal dysplasia; T.O. helped in the statistical analysis; H.N. supervised this study and wrote part of the manuscript; S.K. managed the conduct of this study. All authors read and approved the final manuscript.

References

1 Lachman RS. *Taybi and Lachman's Radiology of Syndromes, Metabolic Disorders and Skeletal Dysplasias*, 5th edn. Mosby, Philadelphia, 2007.
2 Spranger WS, Brill PW, Poznanski A. *Bone Dysplasias*, 2nd edn, Oxford University Press, New York, 2002.
3 Waller DK, Correa A, Vo TM *et al*. The population-based prevalence of achondroplasia and thanatophoric dysplasia in

selected regions of the US. *Am. J. Med. Genet. A* 2008; **146A**: 2385–9.
4 Orioli IM, Castilla EE, Barbosa-Neto JG. The birth prevalence rates for the skeletal dysplasias. *J. Med. Genet.* 1986; **23**: 328–32.
5 Connor JM, Connor RAC, Sweet EM *et al*. Lethal neonatal chondrodysplasias in the West of Scotland, 1970-1983, with a description of a thanatophoric, dysplasia-like, autosomal recessive disorder Glasgow variant. *Am. J. Med. Genet.* 1985; **22**: 243–53.
6 Pokharel RK, Alimsardjono H, Takeshima Y *et al*. Japanese cases of type 1 thanatophoric dysplasia exclusively carry a C to T transition at nucleotide 742 of the fibroblast growth factor receptor 3 gene. *Biochem. Biophys. Res. Commun.* 1996; **227**: 236–9.
7 Wada K, Nakao H, Fujioka K. Survival of newborns with thanatophoric dysplasia. *J. Med. Pharm. Innov.* 2014; **1**: 1–4.
8 Calongos G, Hori M, Ogino M, Sawai H. A case of thanatophoric dysplasia type I with fetal hydrops in the first trimester. *Case Rep. Obstet. Gynecol.* 2016; **2016**: 1821230.
9 Shiro R, Kimizuka A, Yanagisako Y, Miwa T, Yamada N. [National survey of birth prevalence of bone dysplasias.] Report for the Japanese Ministry of Health and Welfare.1999 (in Japanese). [Cited 20 July 2019]. Available from URL: https://www.niph.go.jp/wadai/mhlw/1999/h1129004.pdf
10 Tsutsumi S, Sawai H, Nishimura G, Hayasaka K, Kurachi H. Prenatal diagnosis of thanatophoric dysplasia by 3-D helical computed tomography and genetic analysis. *Fetal Diagn. Ther.* 2008; **24**: 420–4.
11 Sawai H, Komori S, Ida A, Henmi T, Bessho T, Koyama K. Prenatal diagnosis of thanatophoric dysplasia by mutational analysis of the fibroblast growth factor receptor 3 gene and a proposed correction of previously published PCR results. *Prenat. Diagn.* 1999; **19**: 21–4.
12 Baker KM, Olson DS, Harding CO, Pauli RM. Long-term survival in typical thanatophoric dysplasia type 1. *Am. J. Med. Genet.* 1997; **70**: 427–36.
13 Nakai K, Yoneda K, Moriue T *et al*. Seborrhoeic keratoses and acanthosis nigricans in a long-term survivor of thanatophoric dysplasia. *Br. J. Dermatol.* 2010; **163**: 656–8.
14 Nikkel SM, Major N, King WJ. Growth and development in thanatophoric dysplasia: An update 25 years later. *Clin. Case Rep.* 2013; **1**: 75–8.
15 The Statistics Bureau and the Director-General for Policy Planning of Japan, JAPAN STATISTICAL YEARBOOK, 70, 2019. [Cited 20 July 2019]. Available from URL: http://www.stat.go.jp/english/data/nenkan/68nenkan/zenbun/en68/index_h5.html#71
16 Källén B, Knudsen LB, Mutchinick O *et al*. Monitoring dominant germ cell mutations using skeletal dysplasias registered in malformation registries: An international feasibility study. *Int. J. Epidemiol.* 1993; **22**: 107–15.
17 Rasmussen SA, Bieber FR, Benacerraf BR, Lachman RS, Rimoin DL, Holmes LB. Epidemiology of osteochondrodysplasias: Changing trends due to advances in prenatal diagnosis. *Am. J. Med. Genet.* 1996; **61**: 49–58.
18 MacDonald IM, Hunter AG, MacLeod PM, MacMurray SB. Growth and development in thanatophoric dysplasia. *Am. J. Med. Genet.* 1989; **33**: 508–12.
19 Stensvold K, Ek J, Hovland AR. An infant with thanatophoric dwarfism surviving 169 days. *Clin. Genet.* 1986; **29**: 157–9.
20 Donnelly DE, McConnell V, Paterson A, Morrison PJ. The prevalence of thanatophoric dysplasia and lethal osteogenesis imperfecta type II in Northern Ireland: A complete population study. *Ulster Med. J.* 2010; **79**: 114–8.
21 Barbosa-Buck CO, Orioli IM, Dutra MG, Lopez-Camelo J, Castilla EE, Cavalcanti DP. Clinical epidemiology of skeletal dysplasias in South America. *Am. J. Med. Genet. A* 2012; **158A**: 1038–45.
22 Tonoki H. A boy with thanatophoric dysplasia surviving 212 days. *Clin. Genet.* 1987; **32**: 415–6.
23 OMIM - Online Mendelian Inheritance in Man. *134934 Fibroblast Growth Factor Receptor 3: FGFR3. [Cited 20 July 2019]. Available from: http://www.omim.org/entry/134934.
24 Pediatric Orthopaedic Committee of The Japanese Orthopaedic Association. [The Japanese translation of Nosology and Classification of Genetic Skeletal Disorders: 2010 revision.] *J. Jpn. Orthop. Assoc.* 2013; **87**: 587–623 (in Japanese).