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CASE REPORT

Growth and development in thanatophoric dysplasia – an update 25 years later

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Key Clinical Message

Thanatophoric dysplasia is typically a neonatal lethal condition. However, for those rare individuals who do survive, there is the development of seizures, progression of craniocervical stenosis, ventilator dependence, and limitations in motor and cognitive abilities. Families must be made aware of these issues during the discussion of management plans.

Keywords

FGFR3, survivor, thanatophoric dysplasia.

Introduction

Thanatophoric dysplasia (TD) is considered one of the lethal skeletal dysplasias and is due to de novo changes in the *FGFR3* gene. The characteristic features include large head size, extremely short limbs, and narrow chest with underdeveloped lungs. Among those who are born alive, most die soon afterward due to respiratory failure. As the skeletal findings are quite striking, TD is often diagnosed antenatally on fetal ultrasound. In 1988, MacDonald et al. [1] submitted a manuscript to the American Journal of Medical Genetics describing two unrelated, prolonged survivors with TD, patient 1 and patient 2. At the end of the published article, there was an addendum that stated that patient 1 had died at 5.2 years of age. Patient 2 is still living and is in her late twenties. She is older than the other reported prolonged survivor [2] by a few years. We present her history, skeletal findings, and comment on the natural history of this condition.

Clinical Report

As previously reported, patient 2 was born at 35 weeks gestation after an uneventful pregnancy. She was diagnosed shortly after delivery via radiographs with TD. Mutation analysis of the *FGFR3* gene was done initially as part of a research study, and was recently confirmed in a clinical laboratory. She carries the common TD type 1 mutation, c.742C>T (p.Arg248Cys). Although when younger, she went on outings, her residence has been the Children's Hospital of Eastern Ontario. She is now 28 years of age and her mother remains active in her care.

Respiratory and nervous systems

She was able to breathe independently with supplemental oxygen until 2 months of age, when she acquired a respiratory infection. Cranial imaging demonstrated a small foramen magnum. She went on to have cervicomedullary decompression for this stenosis and also received a ventriculoperitoneal shunt. She managed her own respiration until 4 months of age when she required ventilation support. Between the ages of 8 and 10 years, she could be off the ventilator for up to 8 hours on most days. She then developed increased work of breathing due to restrictive lung disease and could only be ventilator-free for 30-min intervals until age 15 years when she became fully dependent. This was further compromised due to the progression of her craniocervical spinal stenosis, causing a high cervical myelopathy and quadriplegia. A magnetic resonance imaging study at 18 years did not demonstrate any cere-

brospinal fluid flow through the foramen magnum. No further decompression surgeries were attempted. Within the last year, her needs from the ventilator have progressed so that she has now reached the upper limits of tolerable ventilation settings.

At her motor "peak", she was able to feed herself popsicles, give "high-5's", roll, move around on her abdomen, lift her feet so that they could be kissed and position her head so she could use her tongue to play with toys. Her tongue hypertrophied as she used it as an appendage (Fig. 1). A developmental assessment in her late teens rated her social, language and motor skills at between an 8–18 month level. At 21 years of age, she was no longer able to use her limbs, was unable to lift her head and could only turn it to the right. She has some vocalizations that her mom can associate with specific concepts or things and uses winking for communication. She knows her caregivers and makes her likes and dislikes known. The loss of many of her capabilities was attributed to the quadriplegia, although there is a feeling among her care providers that she may have declined cognitively as well.

She had a febrile seizure in infancy and then developed a seizure disorder at age 15, which has been stable with monotherapy, Carbamazepine. The focus originates in the left central/sylvian region with secondary generalization.

Oral and gastrointestinal systems

She is fed orally with purees and thickened fluids and has occasional episodes of constipation for which she in on a bowel regime consisting of medical therapy and enema. She has an intact gag reflex and a formal swallowing study was reported as normal. She has a very high narrow palate and prognathism. Her dentition is irregular but there are no caries.

Genitourinary system

She needs intermittent catheterization due to a neurogenic bladder and is prone to urinary tract infections. She entered puberty in her early teens and menstruates regularly.

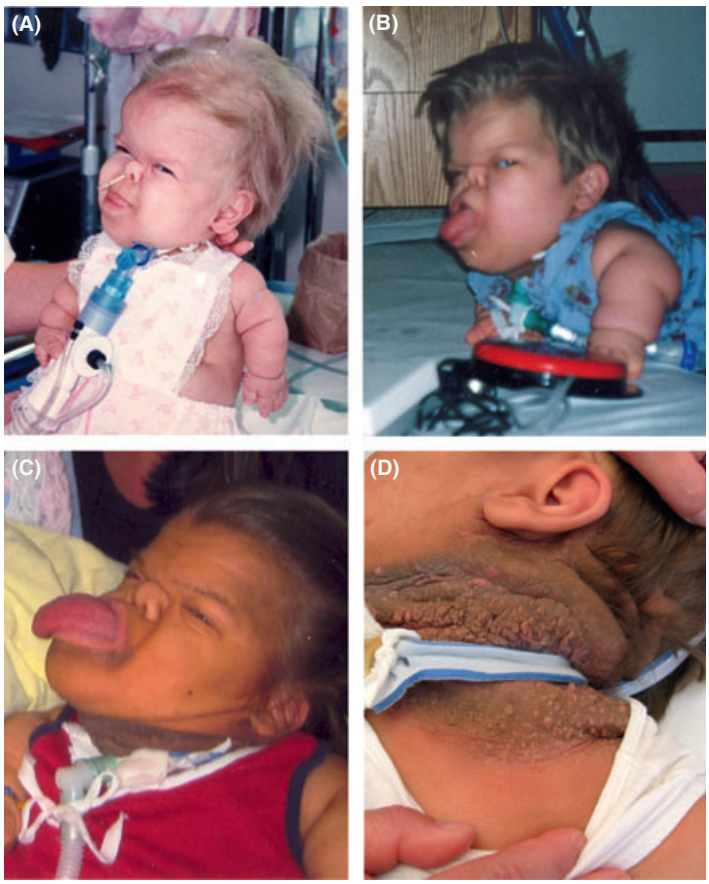

Figure 1. Clinical photos: (A) At age 4 years; (B) In her early teens and at the peak of her motor abilities; (C) At age 22 years with pronounced tongue hypertrophy; (D) Extensive acanthosis nigricans with papillomatous elevations at age 26 years.

Vision and hearing

She has intermittent exotropia. She has a cholesteatoma in her right ear that has been stable in size but has impacted her hearing. She last had her hearing formally assessed in her late teens at which time significant impairment was noted. However, she recognizes voices and reacts to sounds.

Cardiac system

Blood pressure monitoring is extremely difficult as no cuffs fit her anatomy. She had a cardiac arrest at 24 years of age thought to be secondary to a tracheostomy obstruction. A recent echocardiogram demonstrated normal cardiac anatomy and function. She has had episodes of bradycardia noted at night on telemetry, ranging in the low 40's, but no conduction system disease was noted on a Holter monitor study.

Dermatology

In her teen years, she started to develop acanthosis nigricans (AN) in her axilla, groin, and neck. This has progressed into papillomatous elevations around her neck (Fig. 1). She has multiple seborrheic keratoses on her trunk and they are in areas that have not been sun exposed.

Skeletal system

Initial radiographs were classic for TD type 1. More recent films (Fig. 2) demonstrate the evolution of the features. Because she is bedridden, there is significant osteopenia. The bones appear gracile. As there is no weight load on the vertebral bodies, they are tall. There is paucity of growth of the long bones with pronounced widening of the metaphyses. Some of the other features are consistent with those who have *FGFR3* mutations: kyphosis and short vertebral pedicles.

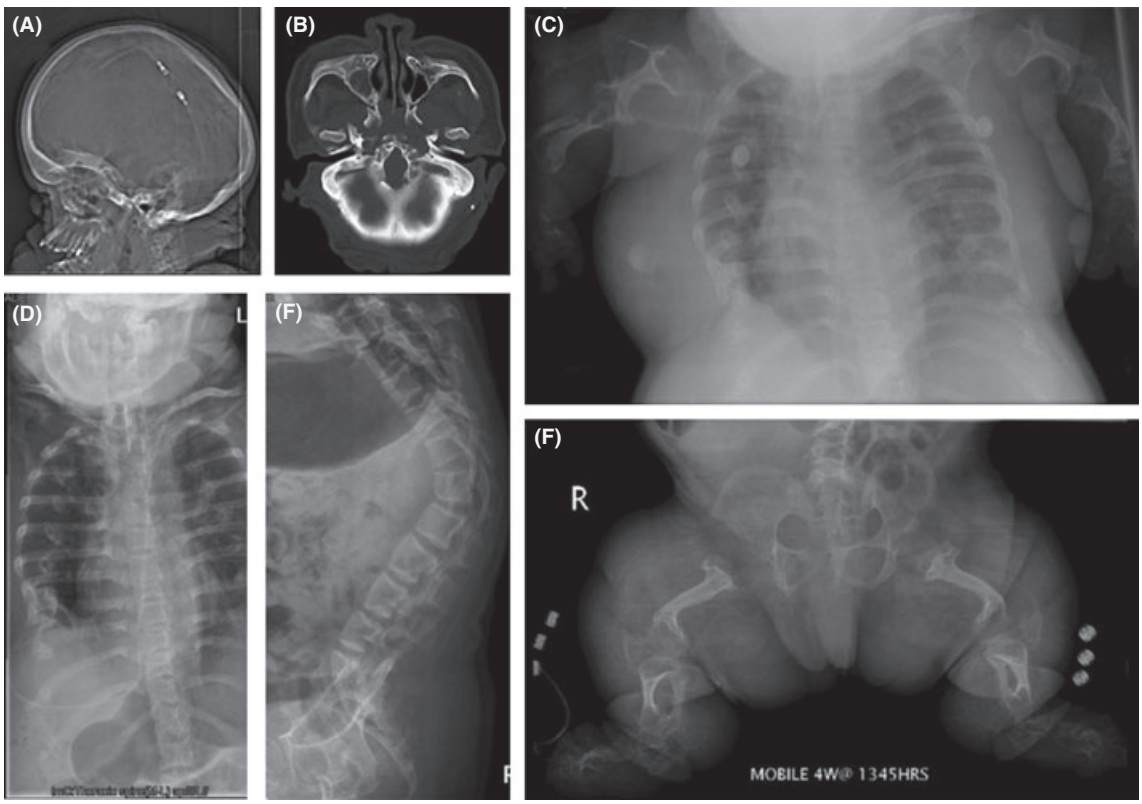

Figure 2. Radiographs: (A) Lateral skull demonstrating macrocephaly, midface hypolasia, shunt placement, and excess skin; (B) Computed tomography at 22 years demonstrating craniocervical spinal stenosis; (C) Chest film including upper limbs – long bones are extremely short and thin with splayed metaphyses; (D) Chest film demonstrating small chest due to short ribs (E) Lateral film at 26 years showing tall vertebral bodies in comparison to depth, short pedicles, and a prominent kyphosis; (F) At 26 years of age, there is osteopenia and a gracile appearance of the pubic bones. The femurs measure 8 cm and the tibias measure 5.7 cm.

Discussion

There is limited information about survivors of presumable "lethal conditions". As the term implies, without medical intervention, the natural history of the condition results in death. For those who follow an atypical presentation, breathing independently for example, medical management is often fraught with ethical dilemmas. However, from individuals who survive long-term, we are able to learn more about the evolution of the phenotype and the development of other features.

There are few case reports on TD long-term survivors [2–5] and they only include those with the type 1 phenotype due to either the Arg248Cys or Gly370Cys mutations in *FGFR3*. The cerebral cortex is malformed in TD, with features comprising of megaloencephaly, hippocampal dysplasia, polymicrogyria, and can include heterotopias [6]. Thus, poor cognitive abilities and the development of seizures are not unexpected outcomes. Additional difficulties may arise due to complications of hypoxia secondary to respiratory insufficiency. Our patient appeared to have a decline in her cognitive abilities in her twenties. However, this coincided with the progression of her craniocervical spinal stenosis, which made it difficult to assess her.

The long bone growth in TD is severely impaired. The disproportionate body with a very large head, average trunk, and short limbs makes mobility very difficult. The ligaments are loose, which results in very hypermobile joints. The inability to weight-bear and resulting osteopenia is likely a unique feature of TD, as premature osteoporosis does not appear to be a complication of other *FGFR3* conditions where there is mobility.

The age of presentation of AN appears to be mutation-specific and those with the Gly370Cys TD mutation developed AN by age two [4, 5], while the earliest presentation for those with the Arg248Cys mutation was age 6 years [7]. Seborrheic keratosis appears to be a later dermatological manifestation in TD and was seen in our patient and the 23-year-old individual reported by Nakai et al. [2], but was not reported in the younger survivors.

Episodes of bradycardia were noted in our patient and in the patient reported by Baker et al. [3]. However, an etiology for these events has not been determined. FGFR3 has low expression in the heart, suggesting that the mechanism is noncardiac in origin.

Palliative care is often in the management plan for those who are born with TD. No long-term survivor has gone off ventilator support, and dependency increased with age in our patient. Developmental skills appear to plateau at an 18-month level, however, excluding this report, only Baker et al. [3] commented formally on language, social, and motor abilities. It is important for families to be aware of the later manifestations of TD when aggressive management decisions are being discussed for a TD child that is born alive and for them to have an appropriate level of expectations for the child. This information is equally valuable to families when there has been an antenatal diagnosis of TD and guidance is being sought.

Acknowledgments

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Conflict of Interest

None declared.

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