

CASE HISTORY REPORT**ABSTRACT**

Zellweger syndrome (ZS) is a rare autosomal recessive disorder, resulting from an impairment in peroxisome function. It is characterized by craniofacial dysmorphism and neurological abnormalities, and involves several systems, which may complicate dental and anesthesia management. The case of a 7-year-old girl diagnosed with ZS is described with emphasis on oral manifestations, oral rehabilitation under general anesthesia (GA), and home oral care. Apart from the unique features of ZS, she presented with clinodactyly, distinctive palatal vault, Class III malocclusion, missing teeth, microdontia, and delayed dental formation. Dental treatment under GA was conducted with concerns of risk of respiratory insufficiency. Oral home care by the parent and regular recall visits were essential to maintain good oral health. Children with ZS may survive into late childhood. They, however, present multiple health problems that are of special concern for not only the pediatric dentist but also the anesthesiologist. Collaboration with the medical team is essential for optimal care of these patients.

KEY WORDS: anesthesia/sedation, developmentally disabled, dental anomalies

Oral manifestations and dental management of a child with Zellweger syndrome

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Introduction

Zellweger syndrome (ZS), also called cerebrohepatorenal syndrome, is an autosomal recessive disorder caused by mutation in any one of several genes involved in peroxisome biogenesis.¹ It is a prototype of the group of peroxisomal disorders, which is comprised of four different disorders including ZS, neonatal adrenoleukodystrophy (NALD), infantile Refsum's disease (IRD), and rhizomelic chondrodysplasia punctata (RCDP). ZS, NALD, and IRD are clearly distinct from RCDP and are usually referred to as the Zellweger spectrum with ZS being the most severe and the least severe being IRD.² The incidence of ZS is estimated at 1:100,000 live births,³ but identification of milder variants and atypical cases by biomedical means has shown a higher frequency of 1:25,000 to 1:50,000.⁴

Patients with ZS are characterized mainly by their typical craniofacial dysmorphism and neurological abnormalities.⁵ The craniofacial dysmorphic features include a high forehead, large fontanelles, hypoplastic supraorbital ridges, epicanthal folds, flat and broad nasal bridge, external ear deformities, micrognathia, and high arched palate.⁵⁻⁹ The neurological abnormalities include severe hypotonia, abnormal Moro reflex, hypo- or a-reflexia, epileptic seizures, and psychomotor retardation.⁵⁻⁹ Other organs are usually affected including the eye (brush-field spots, corneal clouding, cataracts, glaucoma, optic nerve dysplasia, and retinal anomalies), the liver (hepatomegaly, fibrosis, cholestasis), and the kidney (cysts).⁵⁻⁹ Children present, in the newborn period, with profound

hypotonia, seizures, and inability to feed. There is absence of neonatal and deep tendon reflexes and little spontaneous movement.^{9,10}

The diagnosis of ZS is usually based on the classic clinical manifestations. The clinical diagnosis can be supported by demonstration of elevated plasma and tissue levels of very-long-chain fatty acids, phytanic acid, pipercolic acid, and bile salt precursors. Decreased plasmalogen synthesis is also noted.⁶ In case of a high-risk pregnancy, prenatal diagnosis is possible using immunoblotting of peroxisomal β -oxidation enzymes in cultured amniocytes.¹¹ Due to the severe hypotonia, ZS must be distinguished from Down syndrome, Prader-Willi syndrome, and spinal muscular atrophy.^{6,10}

Currently, there is no curative therapy available for ZS. The prognosis of ZS is poor, with death mostly during the first year of life. Death is usually secondary to progressive apnea or respiratory compromise from infection. Other treatment is symptomatic and supportive.¹² Although numerous reports of ZS have been presented in medical literature, the information of oral and dental manifestations is scarce and only high arched palate and micrognathia are frequently mentioned. In addition, although ZS involves several organs, which may complicate dental treatment, so far no reference to dental management of ZS has been found. This paper aims to describe oral findings and dental management with special reference to use of general anesthesia (GA) in a child with ZS.

Case report

The patient was a 7-year-old girl from Northeast Thailand. Wheeled in a pram by her mother, she attended the Pediatric Dentistry Clinic, Faculty of Dentistry, Khon Kaen University, because of dental caries and poor oral hygiene. The patient was the first-born of the family, which had no history of any hereditary diseases and no consanguinity. Both parents and her 6-year-old brother were of normal stature and were healthy. Her weight (12 kg) and height (97 cm) were the average weight and height of 2-year-old and 3½-year-old Thai children, respectively.

Medical and dental history

Her hospital record showed that she was born to a 28-year-old mother and 30-year-old father at 37-week gestation after normal pregnancy. Her birth weight was 3,100 g. Multiple congenital anomalies presented at birth, including hypotonia, facial dysmorphism, and hypertrophic cardiomyopathy with patent ductus arteriosus. In the neonatal period, she was treated with oxygen supplementation for 1 month because of asphyxia. Apart from that, she had senso-



Figure 1. Typical craniofacial dysmorphic features seen in the patient.

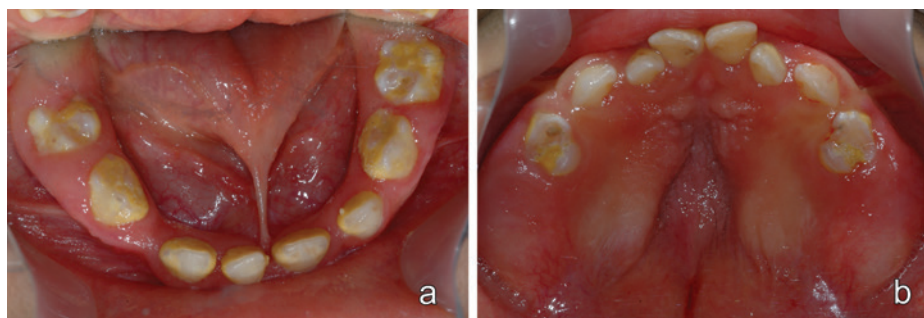


Figure 2. Intraoral appearance showing heavy plaque and calculus deposits, delayed eruption, (a) ankyloglossia, spacing and missing mandibular incisors, (b) crowding maxillary incisors and distinctive palatal morphology.

rineural hearing loss, severe psychomotor retardation, delayed development, and chronic bronchiectasis. She also had severe feeding difficulties and a marked failure to gain weight. At the age of 7 months, she was referred to Chulalongkorn Hospital, Bangkok, where a diagnosis of ZS was made. Congenital hypothyroidism had been diagnosed at the age of 11 months and has been treated with Eltroxin® (thyroxin). Seizures began at 2 years of age and have been controlled by lamotrigine, Dilantin® (phenytoin) and phenobarbital until the present. She had frequent hospital admissions due to recurrent aspirations and viral pneumonia, diarrhea, and failure to thrive. At the age of 4 years, she had gastrostomy and tracheostomy with insertion of tubes. Her current medications consist of phenobarbital, Dilantin®, lamotrigine, and Bactrim® via gastric tube.

The patient was first seen by a dentist at 6 years old and only oral hygiene care instruction for the patient was given to her mother.

Examination

On physical examination, the patient breathed spontaneously through the tracheostomy tube, lay immobile, and was extremely hypotonic. She was unable to sit unsupported and to speak. She had typical dysmorphic facial features: dolichocephaly, prominent forehead, hypertelorism, shallow supraorbital ridges, epicanthus, flat and broad nasal bridge, anteverted nostrils, long philtrum, micrognathia, protruding tongue, and low-set and posterior angulated ears (Figure 1). She also had impaired hearing and limitation of extension of knees and elbows. Both of her first fingers were relatively long and clinodactyly.

Intraoral examination revealed the primary dentition with generalized heavy deposition of plaque and calculus, especially on the mandibular teeth (Figure 2). The maxillary and mandibular arch forms were U-shaped. She had ankyloglossia and generalized spacing of mandibular teeth due to missing primary mandibular incisors (Figure 2a). The

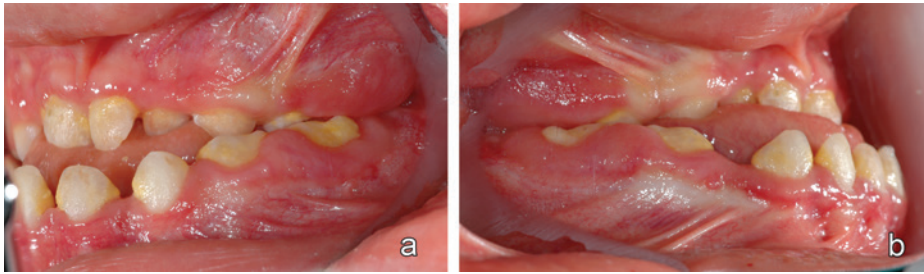


Figure 3. Right (a) and left (b) occlusion displaying Class III malocclusion with anterior open bite.

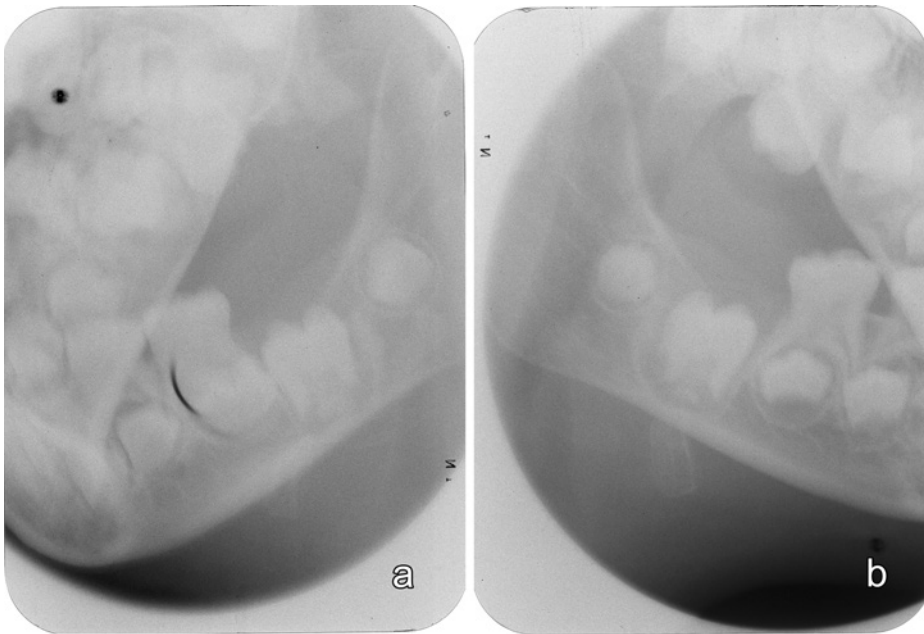


Figure 4. Right (a) and left (b) lateral jaw radiographs showing delayed dental development and microdontia of second permanent molars.

palatal vault had characteristic morphology. Its dimension was short in depth. The lateral part of the vault was low in height while the middle part had a high dome-like shape (Figure 2b). The maxillary incisors were crowded. The primary canines and first molars had not fully erupted. The eruption of all primary second molars was delayed with the primary maxillary second molars unerupted and the mandibular ones only partly erupted. Although her oral care was very poor, carious lesions were found only on the palatal surfaces of both maxillary central incisors and occlusal surfaces of both maxillary first molars. She had Class III malocclusion with anterior open bite, probably resulting from maxillary hypoplasia and placement of her hypo-

tonic tongue (Figure 3). The radiographs, taken under GA confirmed the above-mentioned findings and revealed the delayed dental development and microdontia of mandibular second permanent molars (Figures 4 and 5).

After discussion between a pediatric dentist, a pediatrician, an anesthesiologist, and the mother concerning the patient's severe disabilities and medical risks, oral rehabilitation under GA was decided.

Anesthetic and dental management

The patient was admitted the night before the day of operation. Intravenous

fluid administration was given in the pediatric ward. At the operating theater, routine monitors, including blood pressure cuff, electrocardiogram, and pulse oxymetry were placed. She was premedicated intravenously with atropine 0.1 mg and fentanyl 15 µg. After sevoflurane gradually induced her to sleep via silver tracheostomy tube, end-tidal carbon dioxide, and temperature monitors were attached. The airway was secured by a flexible endotracheal tube size 5.0 mm internal diameter. Anesthesia was maintained with sevoflurane in oxygen/air mixture. Controlled ventilation mode without muscle relaxant was used until the end of the intra-oral procedures.

After anesthetic induction, a throat pack was placed. Dental procedures consisted of radiographs, full mouth scaling and prophylaxis, placement of composite restorations on maxillary central incisors, preventive resin restorations on maxillary first molars and sealant on mandibular first molars, and full mouth fluoride varnish application. Then the throat pack was removed. However, her respiration and consciousness did not fully recover to the baseline status. Therefore, with continuously controlled ventilation, she was taken to the postanesthesia care unit (PACU) where the flexible endotracheal tube was changed to a portex tracheostomy tube with cuff. After 2 hours in the PACU, her vital signs became stable but she could not breathe by herself. Therefore, we moved her to the pediatric intensive care unit (ICU) for postoperative monitoring.

By evening, with regaining of consciousness, the respiration mode was changed to pressure support and she could breathe independently. The ventilator was then disconnected on the next morning. Two days after the operation, she was discharged. Before leaving the hospital, the mother was given the following instructions¹³ for her daughter's regular oral hygiene:

- (1) Positioning: The patient should be propped up at a 45° angle with a bib placed around her neck. The mother should be at the patient's side, either standing or sitting, for the purposes of placing an arm around the

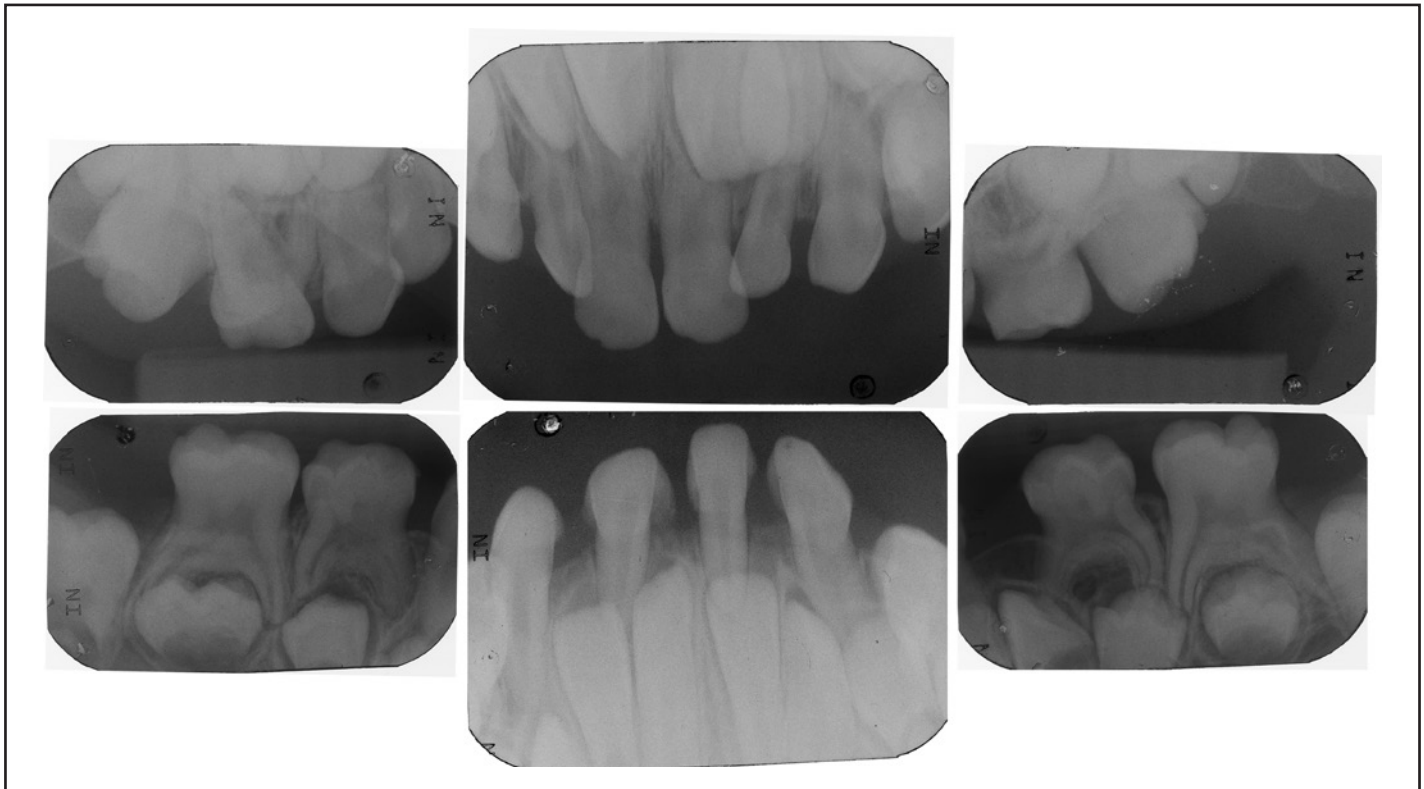


Figure 5. Periapical radiographs presenting crowding maxillary incisors, heavy calculus deposits, missing mandibular incisors and delayed molar eruption.

patient's head to hold it slightly forward, to facilitate drainage of saliva and to retract lip and cheek with fingers as needed.

- (2) Procedure: Use a small amount of fluoride toothpaste on a slightly dampened toothbrush to brush the patient's teeth using scrub technique in an orderly sequence. Then, use clean cloth to wipe toothpaste residue from the mouth without mouth rinsing with water, in order to avoid the patient aspirating fluid with risk of choking. Finally, wipe the patient's face and apply Vaseline to the lips as needed.

After 2 days' postoperative assessment, the patient was placed on 3 months follow-up. At the 6-month recall visit, all restorations were intact. Although her mother did follow the oral hygiene instructions, the deposition of plaque and calculus, and gingival inflammation still occurred. The patient then regularly received hand scaling, prophylaxis, and topical fluoride application. Oral hygiene instruction to the mother was reinforced.

Discussion

Although most cases of ZS are lethal in early childhood, there are now several reports of survival into late childhood and adulthood.^{14,15} This patient has survived longer than usual because she may have a milder variant of ZS and has had generally good care by her mother and the efforts of the modern medical team. However, she is totally dependent and has had multiple hospital admissions due to several problems including pneumonia, diarrhea, secretion obstruction, infection, and failure to thrive.

This patient illustrated several features that are characteristic of ZS. Her distinctive palatal morphology, however, differed from high arched palate, frequently mentioned in previous reports.^{6-8,14} Camptodactyly is another feature found in ZS¹⁶ but this patient had clinodactyly thumbs. She also presented other features, which have never been documented in ZS. These include congenitally missing teeth, malocclusion, and delayed dental development. She was at an average dental age of a 2-year-old

child if considering the tooth eruption and at an average age of a 5-year-old child with respect to the calcification of developing permanent teeth.¹⁷ This may result from hypothyroidism.¹⁸

Although this patient has mild dental problems, oral rehabilitation under GA was decided because of several underlying problems. In conducting anesthesia for children with ZS, the anesthesiologist has several major concerns. These children often present with respiratory insufficiency secondary to severe hypotonia, apnea, and gastro-esophageal reflux with recurrent pneumonia. Before any procedure, pulmonary status has to be carefully assessed.¹⁹ This patient's lungs were clear. We planned not to use muscle relaxant in this patient because it might cause respiratory insufficiency. In addition, its use for intubation was not needed because she had a tracheostomy tube placed and the dental procedures did not require full relaxation. Nevertheless, if necessary, use of a short-acting, nondepolarizing muscle relaxant

that is not metabolized in the liver could have been considered.¹⁹ She also did not receive any sedative premedication. Sedative premedication is not recommended for ZS children because of the risk of airway obstruction due to preexisting hypotonia.¹⁹ For this patient, we used fentanyl because it is short-acting, and without active metabolite. Patients with preexisting respiratory muscle weakness can have an increased sensitivity to the respiratory depressant effects of anesthetic agents.²⁰ This patient presented hypoventilation and delayed recovery, which required careful postoperative observation and the overnight mechanical ventilation in pediatric ICU until the respiratory muscle could function normally.

This patient, although having only mild caries, had generalized heavy deposition of plaque and calculus. Patients fed via gastric tube may not be prone to dental caries because of no exposure to diet. However, the completely absent or greatly diminished swallowing reflex can result in salivary stagnation with an associated development of heavy plaque and calculus deposition leading to periodontal disease.¹³ In addition, special-care-needs children with gastrostomy have significantly more of one aspiration-pneumonia-associated microorganism in saliva, as well as more calculus and plaque, than mouth-fed children.²¹ Thus, prevention is crucial. This patient requires frequent dental follow-up for scaling and oral prophylaxis because of rapid formation of calculus. Home-care regimen includes regular flossing and brushing with a soft-bristled toothbrush and fluoride toothpaste.

Conclusion

This case report shows that it is possible for children with ZS to survive at least into later childhood. The comprehensive dental care for these children can be difficult because they possess several medical and dental problems. Therefore,

the collaboration with medical team is essential for the optimal care.

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