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# An Asian girl with a 'milder' form of the Hydrolethalus syndrome

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**Hydrolethalus syndrome is an autosomal recessive disorder characterized by hydrocephalus, micrognathia, limb anomalies and several other abnormalities, mostly in the midline structures. The syndrome was first described in Finland, where the incidence is approximately 1 in 20 000. All of the Finnish patients were stillborn or died during the first day of life. Only three non-Finnish cases have survived beyond the neonatal period. Here, we report the first Oriental girl with a 'milder' form of hydrolethalus syndrome. The patient died at age 44 days making her the fourth reported case surviving beyond the neonatal period. The case supports the concept of a 'milder' form of the syndrome. Whether this spectrum is due to allelism or locus heterogeneity awaits molecular analysis.**
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## INTRODUCTION

Hydrolethalus syndrome is an autosomal recessive disorder characterized by severe prenatal onset hydrocephalus, a 'key hole-shaped' foramen magnum, hypoplastic eyes, a broad nasal root, cleft palate, malformed low-set ears, micrognathia, limb anomalies, and other abnormalities of the internal organs. It is most common in Finland. Stillbirth or early death is considered to be the rule (Salonen and Herva, 1990). The gene responsible has recently been mapped to chromosome 11q23-25 (Visapaa *et al.*, 1999). Here, we report an Oriental girl with a 'milder' form of hydrolethalus syndrome. The patient had typical craniofacial features except for micrognathia. No internal organ anomalies were found. In addition, the patient survived beyond the neonatal period.

## CASE REPORT

A female infant was born at 39 weeks to a 30-year-old G1P0 Thai mother and a 32-year-old unrelated Thai father. There was no known exposure to infections, teratogenic agents, or other environmental hazards. Serology for HbsAg, HIV, and VDRL were negative. The pregnancy was complicated by polyhydramnios. Ultrasonography performed one day before delivery revealed marked hydrocephalus. A cesarean section was performed because of the large head size and breech presentation. Birth weight was 3650 g. Apgar scores were 5 at 1 min and 7 at 5 min. The placenta appeared normal, weighed 480 g, and the umbilical cord length was 34 cm.

The infant had several anomalies including a markedly enlarged head with head circumference of 42 cm,

aplasia cutis of the scalp (1 cm in diameter) on the left side of the parietofrontal area, frontal bossing, malformed low-set ears, hypertelorism, small and deep-set eyes, a poorly formed and bifid nose, a midline cleft upper lip and a cleft palate (Figure 1). The mandible was not small. Her neck was broad in proportion to her shoulders. Examination of the extremities revealed a right clubbed foot. There was no polydactyly or hallux duplex. Cardiac, pulmonary, abdominal and genital examinations were unremarkable.

A diagnosis of hydrolethalus syndrome was made soon after birth. Genetic counselling was provided to the family. Only supportive care including infant formula feeding through an orogastric tube was given to the patient. The patient remained medically stable for 38 days, then started to have respiratory distress, intermittent cyanosis, apnea, and bradycardia and died at age 44 days.

Chromosomal analysis revealed a normal 46, XX karyotype. Ultrasonography of the head, heart, and whole abdomen performed shortly before the patient died revealed only severe hydrocephalus. No cardiac or urinary tract anomalies were identified. Postmortem skull X-rays revealed an abnormal shape of the opening in the base of skull (Figure 2). Radiographs of the other parts of the body were unremarkable. At autopsy the infant weighed 4700 g. Examination of the calvaria showed widely separated sutures and fontanelles. The bony cleft extended posteriorly from the foramen magnum to form an abnormal shape of the opening in the skull base (Figure 2). The brain weighed 570 g and displayed severe hydrocephalus involving the cerebrum but sparing the brain stem and cerebellum. Upon sectioning, the brain showed a dilatation of the third and lateral ventricles but a normal fourth ventricle. Microscopic examination confirmed the presence of aqueduct stenosis. In addition, thinning of corpus callosum, absence of the septum pellucidum and flattening of cerebral cortex were observed. The left eye was severely microphthalmic and the right eye was absent. The other internal organs were anatomically normal.

Table 1 Features of non-Finnish patients with hydrolethalus-like syndrome

| Features | Present case | Toriello *et al.* (1985) | Aughton *et al.* (1987) |
|---|---|---|---|
| Polyhydramnios | + | + | + |
| Preterm delivery | – | + | – |
| Hydrocephaly | + | + | + |
| Other CNS malformations | Absence of septum pellucidum | Rudimentary olfactory and optic nerve complex. Diffusely polymicrogyric cerebrum and cerebellum | Porencephaly, encephalocele, hypoplastic cerebellar hemispheres, abnormally shaped medulla, absent septum pellucidum, and a partial defect in the corpus callosum, ventricles open to subarachnoid space |
| Abnormally shaped foramen magnum | + | + | + |
| Aplasia cutis | + | – | – |
| Frontal bossing | + | + | + |
| Hypertelorism | + | + | N/A |
| Hypoplastic eyes | + | + | – |
| Malformed low-set ears | + | + | + |
| Poorly formed nose | + | + | – |
| Cleft lip/palate | + | + | Only a small cleft of the secondary palate |
| Micrognathia | – | + | + |
| Preaxial polydactyly | – | – | Both feet |
| Central polydactyly | – | – | – |
| Post-axial polydactyly | – | – | Both hands |
| Club feet | + | – | – |
| Other internal organ involvement | – | Bilateral pulmonary agenesis | Congenital heart defect, genital anomalies |
| Ethnicity | Thai | Black | European/Lebanon/Amerindian |
| Consanguineous family history | – | – | – |
| Age at death | 44 days | 8 minutes | > 5 months |

N/A, data not available.

## DISCUSSION

Hydrolethalus syndrome was first described in the early 1980s (Salonen *et al.*, 1981). Since then, more than 90 cases have been reported (Salonen *et al.*, 1981; Adetoro *et al.*, 1984; Toriello *et al.*, 1985; Aughton and Cassidy, 1987; Anyane-Yeboa *et al.*, 1987; Krassikoff *et al.*, 1987; Bachman *et al.*, 1990; Salonen and Herva, 1990; Pryde *et al.*, 1993; Morava *et al.*, 1996; de Ravel *et al.*, 1999; Visapaa *et al.*, 1999). The majority of them (81 cases) are from Finland, where the incidence has been approximated to be at least 1:20 000 (Salonen and Herva, 1990). All of the Finnish cases were stillborn or died during the first day of life (Salonen and Herva, 1990; Visapaa *et al.*, 1999). The syndrome has been reported in other ethnic groups including Afro-Caribbean, Lebanese, Arab, Mexican, and European. Only three cases survived beyond the neonatal period (Table 1).

Hydrolethalus syndrome is currently a clinical diagnosis. Here we report an Oriental female patient who had several major anomalies consistent with the syndrome including severe hydrocephalus from aqueductal stenosis, the 'key hole-shaped' foramen magnum, absence of septum pellucidum, hypoplastic eyes, low-set malformed ears, cleft lip and palate and club foot. However, the patient seemed to have a milder form of the disorder. She did not have micrognathia, previously claimed to be present in 100% of the syndrome. Cardiopulmonary, gastrointestinal, urinary and reproductive systems in this patient were anatomically normal. A previous review article reported congenital heart disease in 46% of patients, defective lobulation of the lungs 62%, abnormal larynx/trachea 58%, urinary tract anomalies 16%, and uterus duplex in females 52% (Salonen and Herva, 1990). In addition, the patient died at age 44 days. There have been only three previously reported cases of hydrolethalus where the infant survived beyond the neonatal period (Aughton and Cassidy, 1987; Anyane-Yeboa *et al.*, 1987; de Ravel *et al.*, 1999). All of them were non-Finnish. Features of non-Finish cases with a milder

| Anyane-Yeboa *et al.* (1987) | Morava *et al.* (1996) | de Ravel *et al.* (1999) |
|---|---|---|
| N/A | – | + |
| – | – | – |
| + | + | + |
| A Dandy-Walker malformation, absent olfactory bulbs | A Dandy-Walker malformation, agenesis of corpus callosum, absence of cerebellar vermis | A Dandy-Walker malformation, cerebellar hypoplasia, absent corpus callosum |
| – | + | N/A |
| – | – | – |
| + | – | – |
| + | N/A | N/A |
| – | – | – |
| + | Low-set but not malformed | – |
| + | – | – |
| + | – | – |
| + | + | N/A |
| Both feet | Right hand and both feet | – |
| Left hand | – | – |
| – | Right foot and left hand | – |
| – | – | – |
| Accessory spleens | – | N/A |
| Arab | Hungarian | Portuguese/German/South African |
| + | – | – |
| 17 days (1st case) and 4 months (2nd case) | 5 days | 7 months |

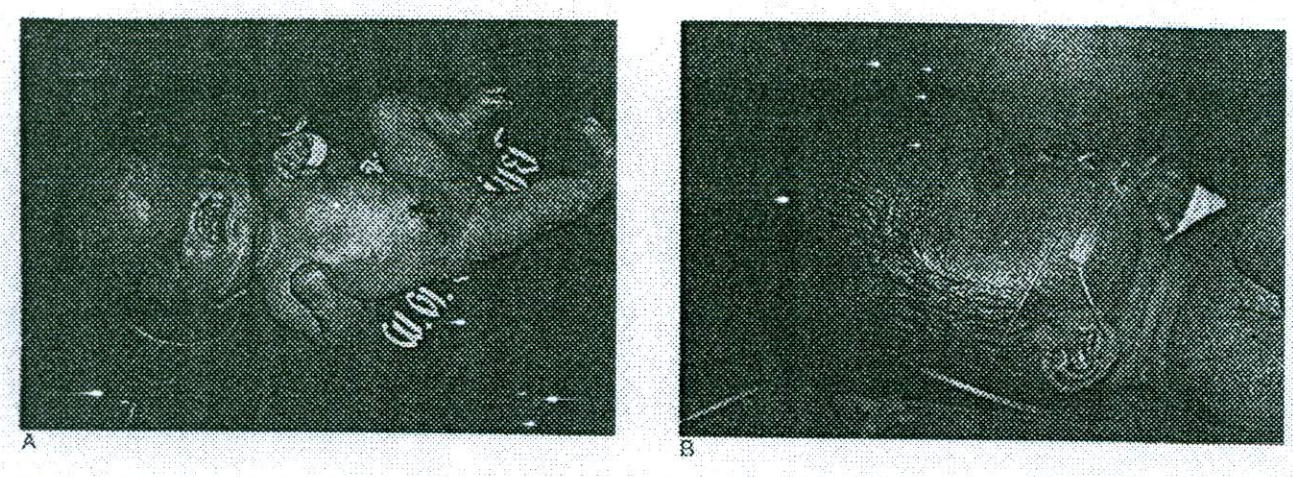

FIGURE 1. The proposita at 1 day of age. (A) Macrocephaly, aplasia cutis, hypertelorism, hypoplastic and deep-set eyes, poorly formed and bifid nose, midline cleft upper lip, broad neck and right clubbed foot. (B) Lateral view of the right side of the face showing low-set ear. The mandible was not small

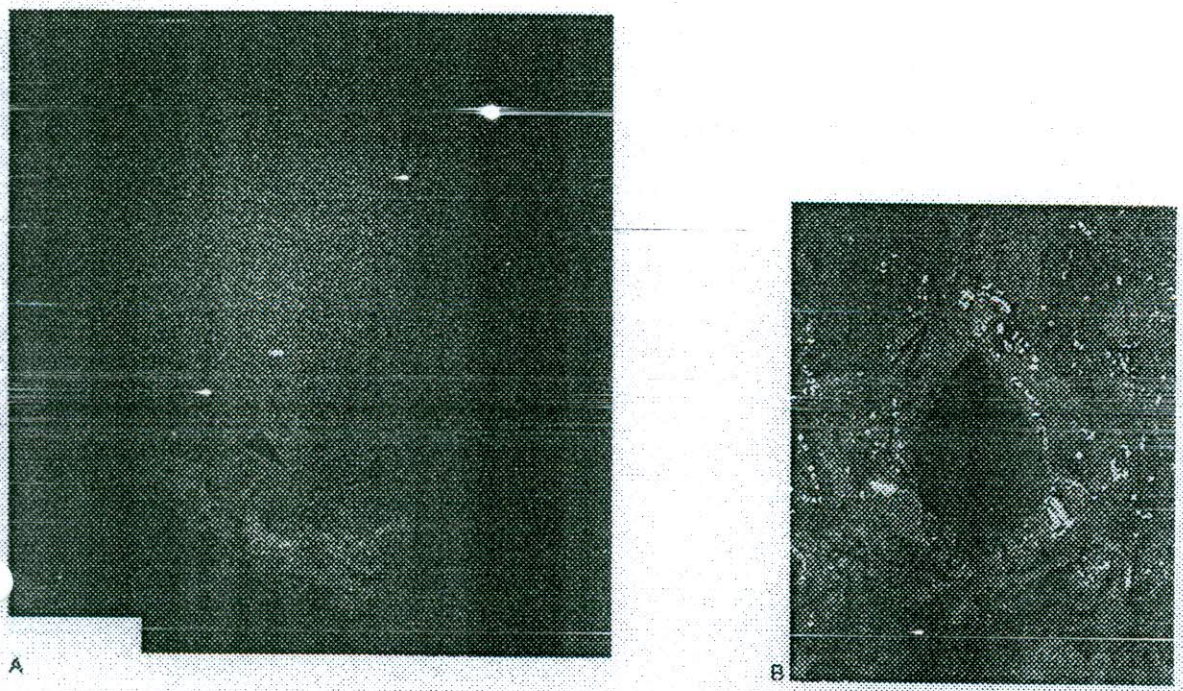

FIGURE 2. (A). The radiograph of the skull in Towne's view reveals markedly enlarged and thin calvarium. The 'key-hole-shaped' foramen magnum is outlined in dots and indicated by arrowheads. (B). Gross specimen of the skull base reveals the abnormal shape of the foramen magnum. The top of the photograph is the posterior part of the skull

form of hydrolethalus syndrome are presented in Table 1. Hydrolethalus syndrome has been proposed to be inherited in an autosomal recessive manner based on a few cases of consanguinity and several families in which there was recurrence in siblings (Krassikoff, 1987). However, history of consanguinity was denied in our family.

The absence of a posterior encephalocele, polydactyly, and cystic dysplastic kidneys in our patient make the diagnosis of Meckel syndrome unlikely. Acrocallosal syndrome is also unlikely due to the absence of polydactyly and the presence of hydrocephalus in our patient. In addition, our patient's features were not consistent with any other known syndromes. Another possibility is our patient represents a distinct syndrome with major features including aqueductal stenosis, microphthalmia, and median cleft lip.

This case supports the concept of a 'milder' form of the syndrome and the founder effect in the Finnish population for the severe form. Whether this spectrum is due to allelism or locus heterogeneity awaits molecular analysis.

## ACKNOWLEDGEMENTS

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