Editorial Commentary

Vosoritide therapy in children with achondroplasia under 5 years of age

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Achondroplasia (ACH) is one of the most common forms of skeletal dysplasia characterized by short-limbed short stature, macrocephaly with frontal bossing, midface hypoplasia, exaggerated lumbar lordosis, limited elbow extension, and trident hands. The estimated global birth prevalence of ACH is reported to be 4.6 per 100,000 (1). ACH is caused by heterozygous gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which is a negative regulator of longitudinal bone growth (2). The average final height of patients with ACH ranges between 127–134 cm in males and 120–125 cm in females (3-6). Disproportionate short stature in ACH is not only a cosmetic problem but also a physical and psychosocial issue. We previously examined the health-related quality of life (HRQOL) of adolescent and adult patients with ACH using the Short Form-36 (SF-36) and demonstrated that patients who were 140 cm or taller showed significantly higher physical function scores than shorter patients (7). Thus, the treatment strategy for short stature in ACH should aim to achieve a final height of 140 cm or taller. Although growth hormone (GH) treatment has been approved in some countries, its effect on growth promotion is transient (5). Extensive surgical limb lengthening is another option to achieve the target height in ACH; however, the procedure requires prolonged treatment and is associated with high rates of complications (8).

Patients with ACH have a high prevalence of disease-specific medical complications throughout their whole life, including upper airway obstructive apnea, foramen magnum stenosis (FMS), hydrocephalus, developmental delay, recurrent otitis media and deafness, thoracolumbar kyphosis, limb bowing, malocclusion, obesity, hypertension, and spinal canal stenosis (SCS) (9-12). Multidisciplinary interventions are required to treat these complications (*Figure 1*). Upper airway obstructive apnea and FMS are two major issues associated with increased mortality in early infancy. Infants with ACH have an increased risk of sudden unexpected mortality due to upper airway obstruction (obstructive apnea) or craniocervical stenosis (central apnea). Narrow nasal passages or choanal stenosis due to midface hypoplasia, relative adenoid and tonsil hypertrophy, and airway muscle hypotonia predispose patients with ACH to obstructive apnea. Some patients require airway surgeries, such as adenotonsillectomy, after polysomnographic evaluation of apnea. Moreover, children with ACH experience premature spheno-occipital bone synchondrosis closure, leading to FMS (13,14). In infants with ACH, the foramen magnum is significantly

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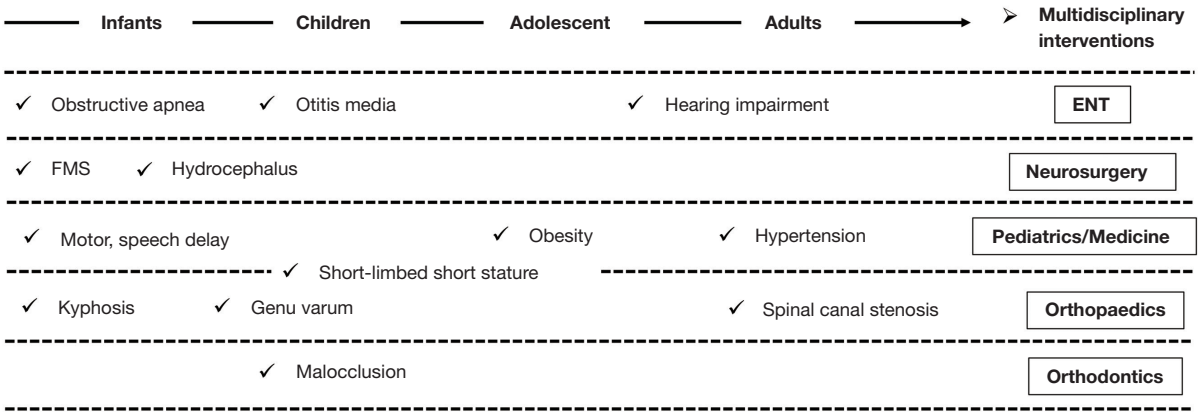

Figure 1 Diseases-specific complications requiring multidisciplinary interventions in ACH. ACH, achondroplasia; FMS, foramen magnum stenosis; ENT, ear, nose, and throat.

smaller than that in individuals with average stature and is further affected by restricted growth in the first 2 years of life (15). Surgical foramen magnum decompression is recommended in the presence of cord signal changes on magnetic resonance imaging (MRI) or spinal cord indentation along with abnormal neurological signs such as muscle weakness, failure to meet developmental milestones, paucity of overall movement, asymmetric limb motion, clonus, and asymmetric reflexes (16). Cord or nerve root compression caused by SCS and spinal malalignment is another important issue affecting the QOL of patients with ACH during adolescence and adulthood. The volume of the spinal canal in ACH is narrow because of the shortened pedicle and lamina. Ligamentum flavum hypertrophy and degenerative spondylosis exacerbate SCS with age. By the age of 10 years, approximately 10% of children with ACH have neurological signs of claudication and increased reflexes in their legs, while approximately 80% have these signs by the sixth decade of life (17). Our QOL survey showed a decline in physical and mental function in patients who previously underwent spine surgeries such as laminectomy, laminoplasty, and instrumentation surgery (7).

Several drugs that modulate abnormally activated *FGFR3* signaling have recently emerged (18). Vosoritide, a recombinant C-type natriuretic peptide (CNP) analog, was first approved for children with ACH aged 5 years or older in the USA and those aged 2 years or older in Europe (19,20). Administration of vosoritide at a dose of 15.0 μg/kg per day in children aged 5–18 years resulted in a highly significant increase in annualized growth velocity and height Z score after 52 weeks of treatment compared with those receiving placebo (21). However, the safety and efficacy of vosoritide in younger children (<5 years of age) with ACH remain unknown. Savarirayan *et al.* recently reported the results of a phase two clinical trial for vosoritide treatment in children with ACH aged <5 years, dividing them into three cohorts based on age at screening (cohort 1: 24–59 months, cohort 2: 6–23 months, and cohort 3: 0–5 months) (22). The most common adverse events were injection-site reactions and erythema. Serious adverse events occurred in 3 (7%) patients in the vosoritide group (decreased oxygen saturation, respiratory syncytial virus bronchiolitis and sudden infant death syndrome, and pneumonia) and 6 (19%) patients in the placebo group (petit mal epilepsy, autism, gastroenteritis, vomiting and parainfluenza virus infection, respiratory distress, and skull fracture and otitis media). Vosoritide treatment for younger children with ACH was generally well tolerated; however, a 1-year-old boy in the vosoritide group with preexisting upper airway obstruction, multiple respiratory tract infections, and cervicomedullary stenosis died. Careful administration of vosoritide is warranted in infants with serious life-threatening complications. Regarding its growth promoting efficacy, the vosoritide group showed gain in least-squared mean height Z score change of 0.25 and annualized growth velocity of 0.78 cm from baseline, similar to the results of previous studies in children aged 5 years or older. Although standardizing height measurements in infants is difficult, these results suggested that a growth-promoting effect of vosoritide can be expected at all ages before epiphyseal closure. To assess the long-term durability of the response, patients who have received vosoritide since infantile period should be followed-up until reaching skeletal maturity.

Does vosoritide have favorable effects on various disease-

specific complications other than short stature? Can vosoritide improve upper airway obstruction, FMS, or SCS? The effects of vosoritide on these serious complications have a greater impact on the lifelong QOL of patients than short stature improvements (23). Foramen magnum in ACH children is small at birth, and it has a severely impaired rate of growth during the first year, which results not only from abnormal endochondral bone growth but also from premature fusion of the skull base synchondroses (13). Similarly, premature closure of the neurocentral synchondroses of the lumbar vertebra is observed in patients with homozygous ACH as well as in mouse models of ACH (24). Although the exact age of the synchondroses closure around the skull base and spinal canal has not been known in ACH children, administration of vosoritide after synchondroses closure is unlikely to be effective. From this perspective, the findings of the present study, in which the drug was administered to patients younger than 5 years, were extremely significant. The authors compared the effects of vosoritide on skull and brain morphology using MRI and observed the most rapid growth in the youngest children in cohort 3. The comparison between baseline and week 52 of the vosoritide group against the placebo group within cohort 3 showed that the facial volume increased by 44% versus 34%, sinus volume increased by 129% versus 48%, and foramen magnum area increased by 44% versus 25%, respectively. In the older children in cohorts 1 and 2, the magnitude of these changes was smaller, with no apparent differences between the vosoritide and placebo groups, indicating the importance of early therapeutic intervention for upper airway obstruction and FMS in ACH. Long-term follow-up of the present patients is essential not only for obtaining evidence of efficacy for these serious complications during infancy, but also for assessing potential SCS rescue, which was not mentioned in this paper but another significant issue during adolescence and adulthood.

In conclusion, vosoritide treatment in children under 5 years of age had an acceptable adverse profile and a gain in height Z score change from baseline. Administration of vosoritide to children under 6 months of age could ameliorate serious complications, such as upper airway obstruction and FMS, by altering the facial bones and skull base morphology. Long-term follow-up of young children who received vosoritide is extremely important to determine whether administration of vosoritide from an early age can rescue SCS and maintain the QOL of adult ACH patients.

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