Post-print Interpretation of Key Points from the International Consensus Statement on Diagnosis, Multidisciplinary Management, and Lifelong Care of Patients with Achondroplasia

Authors: Sun Wenwen[1,2], Liu Jing[2], Kong Dexian[2,3], Zhang Zhimin[2], , Ma Huijuan[2], ,*

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Abstract

Achondroplasia is a hereditary disease caused by FGFR3 mutations that impairs endochondral ossification. The clinical problems arising from this disease affect patients throughout their entire growth process, profoundly impacting the quality of life of patients and their families while increasing economic burden. Early diagnosis and standardized management can effectively reduce disease mortality. However, significant variations currently exist in management protocols. Therefore, an international expert panel has proposed the 'International Consensus Statement on Diagnosis, Multidisciplinary Management, and Lifelong Care of Patients with Achondroplasia' to promote global standardization of disease management. This article provides a key points interpretation of this consensus to enhance understanding of achondroplasia, improve patient quality of life, and reduce disease mortality.

Full Text

Preamble

Key Points of the "International Consensus Statement on the Diagnosis, Multidisciplinary Management, and Lifelong Care of Individuals with Achondroplasia"

Wenwen Sun[1,2], Jing Liu[2], Dexian Kong[2,3], Zhimin Zhang[2,4], Huijuan Ma[2,5,*]

[1]Graduate School, North China University of Science and Technology, Tangshan, Hebei 063210, China
[2]Department of Endocrinology, Hebei General Hospital, Shijiazhuang, Hebei 050051, China

[3]Graduate School, Hebei North University, Zhangjiakou, Hebei 075132, China
[4]Graduate School, Hebei Medical University, Shijiazhuang, Hebei 050017, China
[5]Hebei Key Laboratory of Metabolic Diseases, Shijiazhuang, Hebei 050051, China

Corresponding author: Huijuan Ma, Chief Physician, Professor; Email: huijuanma76@163.com

Abstract: Achondroplasia is a heritable disease caused by FGFR3 mutations that impairs endochondral ossification. The clinical problems associated with this condition affect patients throughout their growth and development, significantly impacting quality of life for both patients and their families while increasing economic burden. Early diagnosis and standardized management can effectively reduce mortality. However, current management protocols vary considerably. Therefore, an international expert panel developed the "International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia" to promote standardized care worldwide. This article provides a key-point interpretation of this consensus to improve understanding of achondroplasia, enhance patient quality of life, and reduce disease mortality.

Keywords: Achondroplasia; Diagnosis; Management; Lifelong care; Consensus

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Achondroplasia is the most common skeletal dysplasia, affecting nearly 360,000 people globally [1]. Clinical issues such as abnormal spine or cartilage development, cardiovascular risks, and sleep-disordered breathing increase mortality risk throughout patients'lives [2] and pose significant daily challenges. Currently, clinical care pathways and protocols for managing children and adults with this disease vary substantially among clinicians. In July 2021, China developed the "Expert Consensus on Diagnosis and Treatment of Achondroplasia"[3], though it did not elaborate on disease management across life stages and multidisciplinary care. In contrast, an international expert panel of 55 specialists from 16 countries across 5 continents developed the "International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia" [4] based on key challenges and optimal management approaches across major life stages and subspecialty areas, aiming to standardize care globally. This consensus statement represents the first international, expert-driven guidance for multidisciplinary management of achondroplasia patients. Therefore, this article aims to interpret key consensus points to improve understanding of achondroplasia management, enhance patient quality of life, and reduce morbidity and mortality.

The disease is a heritable condition caused by FGFR3 mutations (encoding fibroblast growth factor receptor 3) that impairs endochondral ossification, primarily affecting skeletal growth and resulting in disproportionate short stature [5]. Most patients can be accurately diagnosed through a combination of characteristic clinical features (large head, short limbs, short stature, rhizomelic

proportions, and redundant skin folds) and radiographic findings (characteristic pelvis, short squared iliac wings, narrow sacrosciatic notches, and narrowing of interpedicular distance from L1 to L5) [6]. Molecular diagnosis reveals the Gly380Arg (c.1138G>A) variant in 98-99% of patients and Gly380Arg (c.1138G>C) in 1%. Genetic testing can facilitate rapid diagnosis when clinical symptoms and imaging are atypical or unclear, such as in the prenatal period.

This consensus reached agreement on prenatal screening, consistent with Chinese expert recommendations. Achondroplasia is an autosomal dominant disorder, and recurrence risk for parents' subsequent pregnancies depends on whether the parents themselves have achondroplasia. Prenatal diagnosis is recommended for high-risk fetuses. Since no effective treatment currently exists, prenatal diagnosis is particularly important.

The consensus recommends detecting FGFR3 pathogenic variants through chorionic villus sampling or amniocentesis, or utilizing non-invasive prenatal screening with fetal cell-free DNA extracted from maternal blood, particularly for pregnancies at risk for achondroplasia (e.g., when one or both parents are affected, average-height parents have previously had an affected child, or ultrasound suggests possible disease). Chinese guidelines recommend routine prenatal diagnosis at 9-13 weeks gestation via chorionic villus sampling or at 17-22 weeks via amniocentesis to obtain fetal DNA for analysis based on known FGFR3 pathogenic variants in the family.

The consensus also encourages all adults with achondroplasia (especially when their partner also has a monogenic disorder) to receive prenatal counseling [7]. Clinicians should provide psychological support and information on child management when communicating the diagnosis to parents [8, 9]. Routine complete skeletal surveys are unnecessary for infants suspected of having achondroplasia [10-14]; however, genetic analysis for FGFR3 mutations should be considered for patients with clinical or radiographic suspicion.

Since ultrasound typically cannot clearly demonstrate achondroplasia before 24 weeks gestation [15], if ultrasound before this gestational age shows short limbs, increased biparietal diameter, and a low nasal bridge, clinicians should consider other more severe skeletal dysplasias unless there is a clear family history of achondroplasia when ordering genetic testing.

2. Specific Recommendations by Life Stage

2.1 Pregnancy Stage

This consensus recommends that clinicians provide preconception assessment (including factors affecting pregnancy and delivery safety), pregnancy management, and prenatal care for women with achondroplasia. While these women do not have increased risk of spontaneous preterm birth, induction may be necessary due to maternal factors, with vaginal delivery decided based on clinical circumstances. Due to pelvic characteristics in achondroplasia, delivery after 32

weeks should be via cesarean section, with timing individualized based on clinical situation. When preterm labor risk occurs before 32 weeks, fetal size should be compared with pelvic dimensions to determine delivery mode based on anticipated cephalopelvic proportion (delivery is preferably performed in hospitals with intensive care facilities, rapid blood product availability, and advanced airway equipment) [7]. Given that pregnant women with achondroplasia have lower blood volume than average, even moderate blood loss during delivery can cause hemodynamic compromise, necessitating careful fluid and blood product management. Appropriate environments should be provided for postpartum care (including beds and cribs at appropriate heights and accessible toilet facilities).

Both Chinese and international consensus recommend that pregnancies at risk for fetal achondroplasia should seek immediate prenatal care and counseling upon pregnancy confirmation, with prenatal diagnosis for high-risk fetuses. Indications include family history of achondroplasia, affected parents, previous affected pregnancy, or ultrasound suspicion. Chinese guidelines indicate that if parents are unaffected, recurrence risk is 2%; if one parent is affected, risk is 50%; if both parents have achondroplasia, risk is 75%, including 25% chance of lethal homozygous achondroplasia [16]. Therefore, definitive diagnosis is needed to facilitate accurate prenatal counseling and postnatal management discussions.

2.2 Growth and Development Stage

This consensus recommends regular physical examinations throughout growth, using achondroplasia-specific growth parameter charts (height, weight, and head circumference) for longitudinal monitoring [17-20]. In fetal life, increased head circumference (above 97th percentile), shortened femur (below 5th percentile), and trident hand may be observed [21]. Head circumference should be monitored monthly during the first year [20, 22, 23], with rapid growth suggesting need for neurosurgical evaluation when accompanied by other symptoms like hydrocephalus or cervical myelopathy [24]. This aligns with Chinese consensus recommendations.

Since children with achondroplasia typically develop independence in daily self-care skills later, both consensus statements recommend assessing equipment needs and environmental modifications during each examination to maximize independence, monitoring pain, and providing relevant training (e.g., avoiding early sitting to reduce risk of thoracolumbar kyphosis and preventing positional asphyxiation in car seats) [10, 22, 25-28]. Obesity is a common complication affecting obstructive sleep apnea, genu varum, spinal stenosis, and lordosis, making appropriate weight management according to achondroplasia growth curves important [21]. Healthy lifestyles should be encouraged, emphasizing physical activity and healthy diet to maintain fitness (including fat mass, flexibility, and strength) [9, 23, 29-31]. The consensus specifically notes that body fat percentage can be assessed using dual-energy X-ray absorptiometry [32].

2.2.1 Infancy and Early Childhood Regular follow-up is crucial due to increased lifespan complications, with particular importance on monitoring before age two [11, 24, 33]. Recommendations include: 1) routine vaccinations according to national immunization schedules [34]; 2) parents providing specific growth parameter charts during follow-up [19]; 3) specialists using achondroplasia-specific screening tools to assess gross/fine motor and early communication skills; 4) MRI evaluation of head and spine if developmental delay is observed [23, 25, 33, 35]; 5) guidance on positioning and handling (including avoiding early sitting and selecting appropriate car seats and strollers) while maintaining positive attitudes [9, 36, 37]; 6) regular assessment for cervical myelopathy (including motor regression, delayed milestones, apnea, dysphagia, poor weight gain, clonus, abnormal reflexes, and weakness) [9, 11, 33, 38]. To reduce spinal cord compression at the craniocervical junction, the head and neck should be handled carefully during infancy, with avoidance of sit-walkers or baby slings [21]; 7) monitoring for speech delay and obstructive sleep apnea, with polysomnography completed within the first year if respiratory problems are suspected [9, 11, 23, 39, 40]. Chinese guidelines emphasize that increased central apnea suggests craniocervical junction stenosis requiring monitoring for obstructive sleep apnea, with overnight polysomnography performed promptly after diagnosis [16]; 8) early hearing evaluation with longitudinal monitoring (at least annually in early childhood), noting otitis media and middle ear effusion for early detection and treatment [9, 11, 23]; 9) regular spinal development monitoring and dental assessment [11, 41-43]. Chinese guidelines recommend monthly evaluation for children under three years [16]; 10) timely clinical evaluation for pain or fatigue symptoms. Additionally, Chinese guidelines emphasize equal importance of psychological health, recommending appropriate education and environments to help children adapt to school and society [16].

2.2.2 Adolescence and Adulthood Pain prevalence is high and increases with age, requiring longitudinal monitoring [28, 44]. Overweight and obesity are common in adolescence, necessitating weight monitoring using growth parameter charts. Chinese guidelines recommend using achondroplasia-specific growth curves for weight assessment, combined with nutritional status and BMI evaluation during clinical visits (annual follow-up during growth period, biennial in adulthood), with education on healthy diet, nutrition, psychological support, and exercise programs to maintain active lifestyles [16]. The consensus further recommends that in adulthood: 1) persistent back pain with neurological symptoms (claudication, spasticity, reduced walking distance, bladder/bowel dysfunction) may indicate spinal stenosis, warranting whole-spine MRI and timely treatment [45-48]; 2) nocturnal sleep studies for obstructive sleep apnea [49]; 3) regular blood pressure monitoring (forearm measurement when elbow contractures or rhizomelia prevent upper arm measurement) [50, 51]; 4) earlier routine screening for premature hearing loss due to increased risk [52]; 5) regular pain monitoring and its impact on daily life [28, 44, 45]. Genetic counseling should be provided for older adolescents and adults.

3. Specific Complications

3.1 Foramen Magnum Stenosis

Foramen magnum stenosis is a recognized complication of achondroplasia, with infants often showing a "keyhole" appearance and relatively high risk of hypoxic injury to the medullary respiratory control center [24, 33]. Regular neurological history and examination, craniocervical CT, and polysomnography are recommended during infancy, with multidisciplinary team evaluation by neurology and respiratory specialists. The consensus identifies MRI as the preferred imaging modality for cervical cord compression and suggests considering MRI in asymptomatic infants during the first months to assess the craniocervical junction and foramen magnum size (including whole-brain imaging) [22, 33, 38, 53-58]. Recommendations include: 1) no treatment for asymptomatic ventriculomegaly [57]; 2) further MRI evaluation if neurological assessment is abnormal, suggesting cervical cord compression [33, 59]; 3) foramen magnum decompression for symptomatic cervical cord compression regardless of MRI signal changes [33, 54, 56, 60]. Chinese guidelines note ventriculoperitoneal shunting for increased intracranial pressure and suboccipital decompression for craniocervical compression [16]; 4) neurosurgical evaluation for MRI-confirmed cervical cord compression even without symptoms [24, 33, 54, 60]; 5) MRI signal changes without foramen magnum stenosis are not uncommon in older children and adults and typically require no intervention [60, 61].

3.2 Spinal Issues

Spinal stenosis in the cervical or thoracic spine can cause myelopathy signs, with early symptoms typically being back and buttock pain. Neurological symptoms (lower extremity weakness, impaired mobility, bowel/bladder changes, pathological reflexes) require MRI evaluation [45, 46, 62]. Early sitting is a risk factor for anterior vertebral wedging, kyphosis, and spinal stenosis; forced sitting should be avoided until independent sitting is achieved [21]. Thoracolumbar stenosis can cause neurogenic claudication, managed conservatively with weight loss and physical therapy, with surgery considered for severe symptoms or failed conservative treatment [23, 27]. Thoracolumbar kyphosis is common in infancy and requires regular radiographic monitoring and timely treatment if progressive [27, 42, 63]. Recommendations include: 1) fusion and stabilization during initial decompression in skeletally immature patients (due to risk of post-laminectomy kyphosis with continued growth) [46]; 2) fusion and stabilization in skeletally mature patients undergoing decompression over 5 levels, crossing a junctional zone, or with sagittal malalignment (including thoracolumbar kyphosis) to prevent postoperative deterioration [41, 46, 48]. Chinese guidelines additionally recommend modified thoracolumbosacral orthosis when fixed deformity exceeds 30° on lateral lumbar radiographs, or with significant wedging or vertebral slippage [16].

3.3 Genu Varum

Knee and lower leg bowing present with activity-induced pain and self-limitation of walking and upright activities. The consensus recommends lower extremity clinical evaluation in prone, supine, and standing positions to analyze tibial torsion, alignment, limb stability, and joint flexion [11]. Full-length standing anteroposterior radiographs (hips to ankles, patellae forward) are needed to assess angular deformity [64-67]. Bracing is not indicated for genu varum. Deformities can be corrected via osteotomy or guided growth, with timing and method adjusted based on symptoms, severity, growth pattern, and remaining growth [11, 69]. Surgical indications include persistent periknee pain, instability, and gait changes affecting quality of life [11, 64]. Chinese guidelines also suggest surgery when three weight-bearing joints are not in vertical alignment [16]. For lateral knee pain without angular deformity, MRI is recommended to exclude discoid meniscus [70-72].

3.4 Respiratory Issues

Both consensus and Chinese guidelines recognize upper airway obstruction and obstructive sleep apnea (OSA) as common in childhood, manifesting as apnea, periodic hyperventilation, struggling respirations, difficulty sleeping supine, frequent awakenings, feeding difficulty, and cough. Chronic sleep disruption can affect growth and increase accident risk, while chronic hypoxia increases pulmonary hypertension and cor pulmonale risk [73], making timely OSA identification crucial. Nighttime polysomnography and sleep studies should be completed by age 2 [23, 40, 74-78], with evaluation of midface hypoplasia severity, tonsillar hypertrophy, and nasal patency via multidisciplinary ENT and respiratory assessment. Foramen magnum decompression decisions require comprehensive clinical, radiographic, and polysomnographic evaluation and can improve neurological and developmental outcomes; lack of central apnea on sleep studies is not a contraindication when clinical or MRI criteria are met [33, 77]. Non-invasive positive pressure ventilation treats OSA, with surgery recommended for tonsillar/adenoidal hypertrophy [21]. Tonsillectomy and adenoidectomy are first-line treatments in childhood, with polysomnography repeated 2-4 months postoperatively to assess persistent or recurrent disease [40, 74, 76, 78]. Additional recommendations include: 1) further airway surgery in adults with persistent OSA after adenotonsillectomy [40, 77]; 2) evaluation of alternative treatments like continuous positive airway pressure for children with persistent OSA after upper airway surgery [74, 75]; and 3) respiratory failure risk reduction during infections through passive smoke avoidance, infection avoidance, and monoclonal antibody prophylaxis for respiratory syncytial virus [76].

4. Surgical and Specialty Considerations

4.1 Limb Lengthening

Indications, methods, and optimal timing for first surgery remain undetermined in literature. Multidisciplinary team consultation and evaluation should be performed pre- and post-operatively to consider functional, physiological, and psychosocial outcomes [79-81]. While limb lengthening can increase height by 30-35 cm, serious complications are common [82], including foot drop, residual peroneal nerve palsy, knee/ankle valgus deformity, fracture, ankle contracture, and delayed/nonunion. Preoperative MRI of the entire spine, cervical region, and skull base is mandatory to reduce spinal cord injury risk from neck extension during anesthesia and surgery. Many experts recommend delaying surgery until at least age 12 [83].

4.2 Otolaryngology

Hearing loss and middle ear disease are common in achondroplasia, related to midface skeletal dysplasia, short eustachian tubes, and tonsillar hypertrophy. Comprehensive hearing assessment should be performed at birth (no later than age 5) [9, 23, 52]. Tympanic membrane evaluation and hearing difficulty inquiry should be routine during follow-up for early detection and correction [23, 52]. Chronic eustachian dysfunction causing middle ear effusion and conductive hearing loss is common, hindering language development [52]. Tympanostomy tubes are recommended when effusion persists over 3 months with documented hearing loss [11, 84-86]. Hearing aids are a treatment option [52, 84]. Chinese guidelines suggest standard rehabilitation therapy [16]. High jugular bulbs are common in achondroplasia, requiring careful otoscopic examination before tympanostomy or other otologic surgery [53, 87].

For children with achondroplasia and maxillary arch growth deficiency, orthodontic evaluation is appropriate [88]. Maxillary orthodontic expansion and protraction can increase upper airway capacity if OSA persists after pharyngeal surgery [77, 89]. Orthognathic surgery via Le Fort I or III osteotomy can be considered after skeletal maturity [90].

4.4 Anesthesia

Due to small mouth, large tongue, narrow nares, midface hypoplasia, large adenoids, and short neck with limited mobility, anesthesia should be performed in experienced centers [91]. Head and neck movement should be minimized during mask ventilation and intubation due to foramen magnum stenosis. Airway adjuncts for difficult bag-mask ventilation and video laryngoscopy should be readily available. Preoperative assessment should specifically evaluate airway, neck range of motion, snoring, and sleep-disordered breathing history [91-93]. Central sleep apnea may occur in infants with craniocervical junction compression, with sleep-disordered breathing history guiding post-anesthesia discharge decisions [91].

4.5 Psychological Issues

Achondroplasia diagnosis creates varying psychosocial impacts on individuals, parents, and families [94]. Complications and sequelae impose significant physical and psychological burdens, resulting in poor quality of life. Regular follow-up should include psychological counseling and support to maintain positive attitudes [9, 11, 23, 94-96].

In summary, beyond understanding achondroplasia diagnosis, we must ensure early detection, timely treatment, multidisciplinary lifelong management, and psychological support to minimize burden on patients and families, delay complication progression, and reduce mortality.

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Note: Figure translations are in progress. See original paper for figures.