Achondroplasia in 2018

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ICEOS
Mini-Symposium: CHALLENGES IN TREATING DYSPLASIA
November 15, 2018 1:40-1:49
Outline

• Pathogenesis and Treatment opportunities

• Spine Deformities
Achondroplasia

- Causative gene found (1995) by Bellus, Heffernon
  - Johns Hopkins
- Fibroblast growth factor receptor 3  \( FGFR3 \)
  - 99\% with same \( \text{Gly380Arg} \) substitution; <1\% with \( \text{Gly375Cys} \)
  - Autosomal dominant
  - 100\% penetrant
  - 80-90\% spontaneous mutation
  - Advanced paternal age
  - Molecular prenatal diagnosis available
GAIN OF FUNCTION: mutation associated with an increase in normal functions of protein

NORMAL

FGFs bind to FGFR3

Inhibits proliferation of cartilage cells

ACHONDROPLASIA

FGFR3 mutation

Overactivity of normal growth inhibition

Cartilage cells stop proliferating

Short stature
A: Chondrocyte with mutated FGFR3 that down-regulates its development via the MAPK/ERK

B: Vosoritide (BMN 111) blocks this mechanism by binding to the atrial natriuretic peptide B, which subsequently inhibits the MAPK/ERK path
Medical complications in achondroplasia

• Obstructive sleep apnea
  – Referral to pulmonology, ENT
  – Tonsillectomy / adenoidectomy
  – CPAP

• Central sleep apnea
  – Referral to neurosurgery
  – Foramen Magnum Decompression
Skeletal Dysplasia Spine Summary

- Upper cervical instability
- Kyphosis in Achon
- Scoliosis
- Stenosis- Achon
Achondroplasia Spine

- Early-onset foramen magnum stenosis
  - Some improve spontaneously
  - Suspect if sleep apnea, weakness
  - MRI, sleep study to evaluate
  - Foramen magnum decompression
Achondroplasia Spine Issues

- How to manage kyphosis
- Does bracing work?
- Indications for spine fusion?
- When should you fuse to sacrum?
TL Kyphosis in Achondroplasia

- Characteristic feature
- <1 year: 94% prevalence
- 30% persistent
- Etiology: hypotonia
- T10-L4
- Corrects in prone position
Achondroplasia
-Spinal problems

- Thoracolumbar kyphosis before walking
  - usually resolves shortly after walking
  - If not, L1 may progressively wedge
70% resolved

30% pts with persistent TLK at final FU

- 30% pts ≥40° of persistent TLK
  - (80% symptomatic - PSF)

- 70% pts 20-40° of persistent TLK
  - (15% symptomatic - PSF)
Radiographic Predictors of Persistent TLK

- **Apical vertebral translation:**
  - 5% ($p=0.001$)

- **Apical vertebral wedging for height:**
  - 6% ($p=0.031$)
Clinical Parameters Predicting persistent TLK

Motor delay:
Inability to sit at 14 mos or walk independently
At 30 months

- Sitting: 7 – 14 months
- Walking: 15 – 30 months
Achondroplasia Spine Issues

• Does bracing work?
  – No data on this point; try in late kyphosis

• Indications for spine fusion:
  – Any TL decompression for stenosis in immature patient
    • Otherwise will progress

• For deformity alone:
  – If painful, progressive
  – Most tolerate mild TL kyphosis
Case example – interval improvement

- Age: 14 months
- Sitting Age: 12 months
- Not yet walking

14 months
Kyphosis: 40 degrees
Case 1 – interval improvement

- Age: 14 months
- Walking age: 27 months
- No Brace; kyphosis improved
- Further follow up needed?

14 months
Kyphosis: 40°

4 years
Kyphosis: 40°
Case 1 – recurrence

- 14 yrs: claudication
- Squats after walking
- Temporary foot drop

14 years
Kyphosis: 32° degrees
Case 1 – recurrence

- MRI confirmed stenosis
- Decompression T12-L4
- Instrument kyphosis in immature pts
- Don’t overcorrect

14 years
Kyphosis: 52°
s/p PSF
Achondroplasia - Operative issues

- High risk of IONM changes (~30%)
- Avoid Hooks, instruments in canal
- Pedicle & Screw diameter ok
  - 5-7 mm
  - Length decreased by ~1 cm
- High risk of dural violation
  - Nerve roots seem “pressurized”
Achondroplasia: Operative Issues

• Should you fuse to sacrum?
  – Lower re-stenosis;
  – trend to difficulties with personal care
Case 2
8 yr old with Achondroplasia

- S/P F. Magnum decomp x 2
- Neurogenic Claudication
- MR confirms stenosis
- Recommendation
  - Decompress?
  - Fuse + metal?
  - Levels?
  - Or Wait?
Case 2

- Further surgery needed?
  - *What type*
    - And approach
  - *How far*
  - *What alignment?*
Case 2

- Extension of Fusion to T8
  - Looked good (then!)
Next Steps?

1 yr
4 yrs
6 yrs
Case 2

- Stabilized, no further complaints
- Final AP and lat 4/18
Summary

- 70% of children “walk out of” kyphosis
- Bracing efficacy unknown
- Instrument all adolescent decompressions
- Correct only to prone kyphosis
- Judicious fusion to sacrum

- Geneticist invaluable in monitoring
Thank you!
Resources for Syndromes

• Online Mendelian Inheritance in Man (OMIM)
  – Available through NLM/Pub Med
  – Allows search by findings

• National Organization for Rare Disorders (NORD) (http://www.rarediseases.org/)
  – Includes summaries of rare disorders

• Medical Geneticist
  – Some become “primary care” for syndromes
Thank You
Thank You
Genu Varum (Surgery)

- Preoperative, 1 year, and 2 years radiographs for a 2 year old boy with achondroplasia
Achondroplasia

- Most common skeletal dysplasia
- 1:10,000-1:30,000
- Dwarfism in ancient Egypt, Greece, Rome, ~3,000 to ~30 BCE
- Revered by rulers, general population

[Image of ancient Egyptian figure]

Discovered in limestone tomb in 1989 Western field of great pyramid Khufu
Binding FGF to FGFR3 dimerizes the receptors

Activated FGFR3 ubiquitinated to direct to lysosomes to be degraded; signaling stops
With FGFR3 mutation, dimerization is too stable & too much signaling occurs.

Achondroplasia: transmembrane domains stabilize dimers.

TD1: disulfide bonds in extracellular domain stabilize dimers.

TD2: kinases are activated.

All mutations: kinases activated, hinders ubiquitination. Not degraded.
FGFR3 signaling pathways important in growth plate of chondrocytes

MAPK: Mitogen activated protein kinase. Negatively affects proliferation, terminal differentiation and matrix synthesis (via p38 and ERK)

STAT1: Signal transducer and activator of transcription. Inhibits chondrocyte proliferation.
C-type natriuritic peptide can bind to natriuritic peptide receptor B. Causes accumulation of intracellular cGMP. CNP-NPR-B signals antagonize MAPK signaling.

This is the mechanism of Vosoritide
ACHONDROPLASIA IS A METAPHYSEAL DYSPLASIA

- Normal = A, D
- Epiphyseal = B
- Metaphyseal = C
- Diaphyseal = C
- Spondylo = E
Achondroplasia

Average stature child
SMALL SACROSCIATIC NOTCHES

Average stature child

SQUARE, FLAT Iliac BONES

METAPHYSEAL FLARING

ORTHOPAEDIC SURGERY
OVAL LUCENCY OF PROXIMAL FEMURS

‘ice cream scoopers’

Average stature child
INTERPEDICULAR NARROWING
LUMBAR REGION

Average stature child
SHORT, BROAD CONE-SHAPED PROXIMAL AND MIDDLE PHALANGES

TRIDENT HAND DEFORMITY

Average stature child
Small foramen magnum in achondroplasia

• Cervicomedullary compression
• Central sleep apnea
• Hydrocephalus
• Long track signs (hyperreflexia, clonus, paresis)
  – Monthly OFC on achondroplasia-specific curves, regular complete neurologic exam/developmental assessment
  – MRI, sleep study

ORTHOPAEDIC SURGERY
Other phenotypic features of achondroplasia

- RHIZOMELIA
- MID-FACE HYPOPLASIA
- LUMBAR LORDOSIS
- RELATIVE MACROCEPHALY
- INCOMPLETE ELBOW EXTENSION
- HYPOTONIA
- JOINT LAXITY
UNIQUE GROWTH FEATURES OF ACHONDROPLASIA
BMI is inaccurate surrogate for body fat without more research to define its correlation with body composition.
Dramatic disproportion in upper segment: lower segment at all ages as compared to average stature
Medical Complications, Treatment
Achondroplasia - techniques

• Correct kyphosis only to “best bend”
Medical complications in achondroplasia

• Recurrent otitis, chronic middle ear fluid
  – *Speech delay, hearing deficit*
  – *Screen with annual audiology*
  – *Refer to ENT*
  – *Placement of tubes*
  – **Jugular bulb dehiscence = absence of roof over jugular bulb**
Medical complications in achondroplasia

• Narrow spinal canal, lordosis
  – Nerve compression
  – Pain
  – Decreased endurance
  – Bowel/bladder incontinence
  – Inactivity cycles with overweight/obesity
  – Squatting, weight reduction, decompression
Greenberg Center for Skeletal Dysplasias
Johns Hopkins University
McKusick-Nathans Institute of Genetic Medicine

410-614-0977
Colleen Gioffreda, Program administrator
Julie Hoover-Fong, MD, PhD, Director
Skeletal Dysplasia Spine Summary

- Upper cervical instability in SED, Kneist, MPS
- Kyphosis in Achon, Larsen, Diastrophic (resolving?)
- Scoliosis in SED, Metatropic
- Stenosis: Achon, r.chondrodysplasia punctata
No pubertal growth spurt in achondroplasia
Achondroplasia Spine Cases

John E. Herzenberg

IPOS

BAD TO THE BONE: CHALLENGES IN TREATING DYSPLASIA AND GENETIC SYNDROMES

November 30, 2017 4:05
Known Cartilage Defects

Matrix disorders

No significant effect on matrix
Additional comments about achondroplasia

- Average adult height: male = 51”, female = 48”
- Growth hormone- no significant improvement
- Limb lengthening
- Obesity
- Hypertension
Achondroplasia

- **FGFR3** encodes 1 of 4 FGF receptors
- All FGF receptors have:
  - Extracellular ligand-binding domain
  - Transmembrane domain
  - Intracellular domains

TDI = thanatophoric dysplasia type 1
ACH = achondroplasia
HYP = hypochondroplasia
TDII = thanatophoric dysplasia type 2
SADDAN = severe achondroplasia
developmental delay acanthosis nigricans
Skeletal Findings in Achondroplasia

- Rhizomelia
  - Hindered reach
  - Adaptive equipment

- Thoracolumbar kyphosis
  - Often resolves spontaneously
  - Monitor

- Genu varus, tibial bowing
  - Pain
  - Monitor closely early, osteotomies
1. TLK in relation to walking age

- **Presentation**: Mean: 11 mo.
  - 100% TLK

- **Walking age**: Mean: 21 mo.
  - 15% resolved

- **1 yr after walking age**: Mean: 33 mo.
  - 58% resolved

- **Final FU**: Mean: 7 y/o
  - 70% resolved
Other Clinical Features of Ach

- Midface hypoplasia / relative macrocephaly
- Rhizomelia
- Hypotonia, joint laxity
- Elbow flexion contractures — *No significant effect on function*
- Trident hand
- Increased lumbar lordosis - worsens stenosis
## Associated Clinical Parameters

### Odds of Clinical Factors Predicting Thoracolumbar Kyphosis in 60 Patients With Achondroplasia

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
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<td><strong>Developmental motor delay</strong></td>
<td>4</td>
<td>1.05-15.11</td>
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<tr>
<td>Foramen magnum decompression</td>
<td>1.64</td>
<td>0.42-6.45</td>
<td>0.476</td>
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<td>Hydrocephalus</td>
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<td>0.39-15.15</td>
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<td>Female</td>
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<td>0.43-5.85</td>
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<td>Ventriculoperitoneal Shunt</td>
<td>0.63</td>
<td>0.04-9.58</td>
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CONCLUSION

• Most pts with TLK ≥ 20° improve after 1 year of walking age (58%)

• TLK 20-40° → non-surgical management

• TLK ≥40 ° or symptomatic → decompression and PSF

• Apical vertebral wedging for height and apical translation is associated with persistent TLK

• Developmental motor delay is associated with persistent TLK
Case 1 – improvement

- 14 month old
- Sat 9 months
- Not yet walking
- Kyphosis 33 degrees supine

Discussion:
- Is this a hemivertebra?
- What workup for non-ambulation?
- Rx for Kyphosis:
  - restrict sitting, brace, cast?
Case 1 – Follow up

- Walked 15m
- No brace
- Neuro Nl.

14 months  2 years  3 years  6 years
Case 2 Summary

- **2001**, decompression/laminectomy from L1 to L5 to relieve a lumbosacral stenosis
- fused T12 through S1 with rods and hardware fixation.
- **11/27/01**, there was skin breakdown over the hardware with a dark eschar
  - covered by a rhomboid flap
- **11/29/06** revision and fusion of T-12 to T-8.