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‘Contributing to the Achondroplasia module: a student experience’

EuRREB
European Registries for Rare
Endocrine and Bone conditions

Contributing to the Achondroplasia module: A student experience

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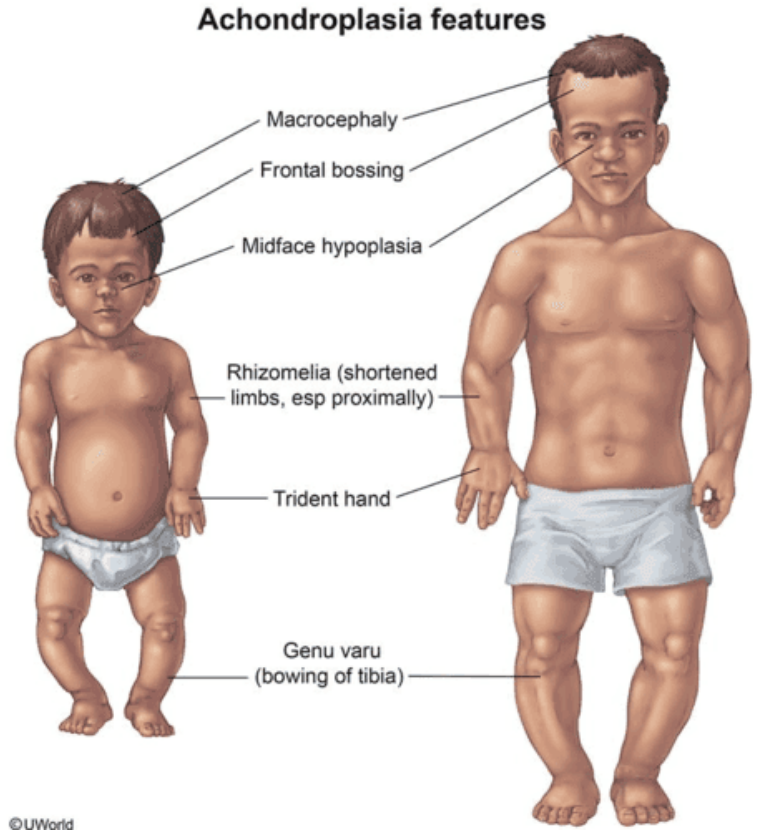
EuRREB
European Registries for Rare Endocrine and Bone conditions

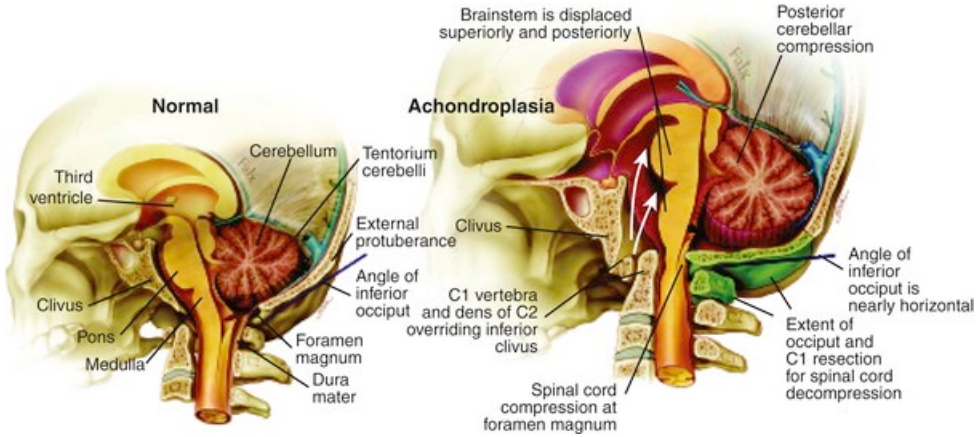
Funded by the European Union

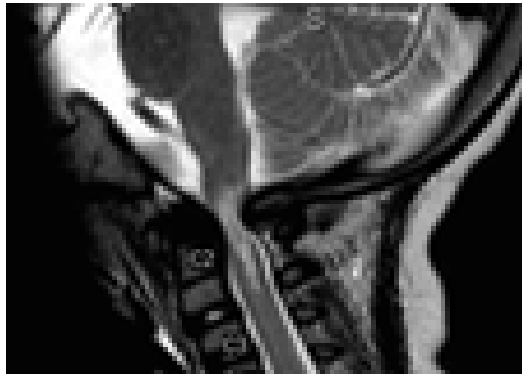
Achondroplasia

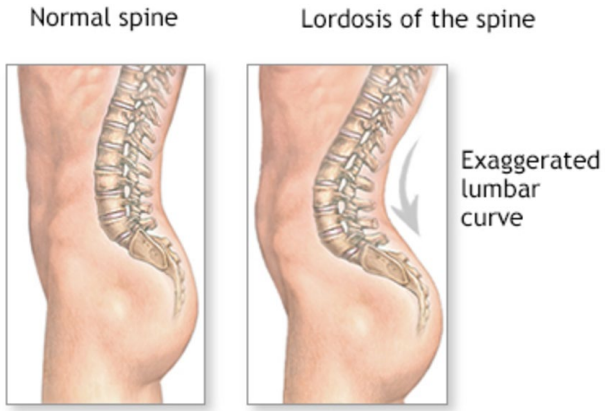
- Most common type of skeletal dysplasia
- Gain-of-function mutation in FGFR3
  - Inhibits endochondral ossification at growth plates
- Clinical characteristics:
  - Short stature
  - Rhizomelic limb shortening
  - Macrocephaly with frontal bossing

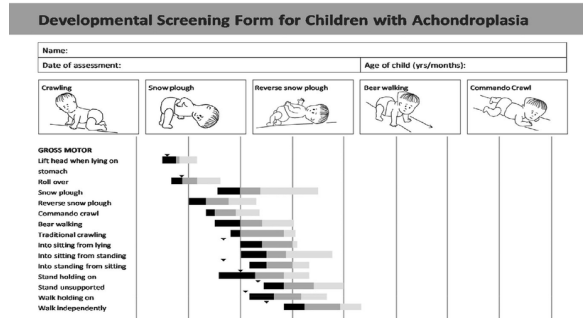


Multisystem complications



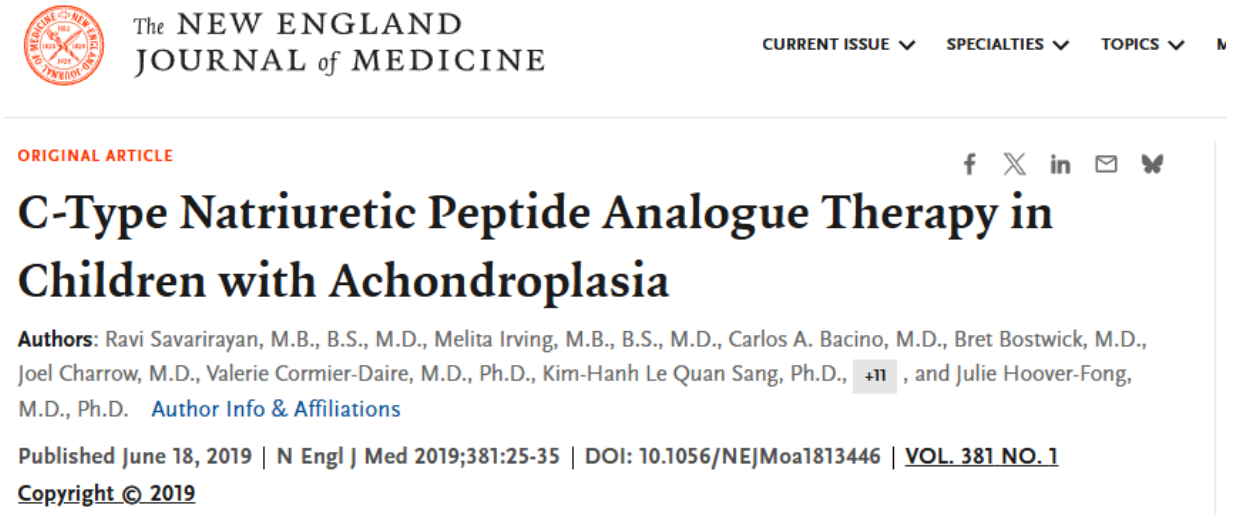






Optimal management requires a coordinated multidisciplinary approach

Vosoritide



The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS M

ORIGINAL ARTICLE

C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia

Authors: Ravi Savarirayan, M.B., B.S., M.D., Melita Irving, M.B., B.S., M.D., Carlos A. Bacino, M.D., Bret Bostwick, M.D., Joel Charrow, M.D., Valerie Cormier-Daire, M.D., Ph.D., Kim-Hanh Le Quan Sang, Ph.D., +11 , and Julie Hoover-Fong, M.D., Ph.D. Author Info & Affiliations

Published June 18, 2019 | N Engl J Med 2019;381:25-35 | DOI: 10.1056/NEJMoa1813446 | VOL. 381 NO. 1

- Vosoritide: Recombinant C-type natriuretic peptide (CNP) analogue → Inhibits overactive FGFR3 gene [1]
- Significantly increases length

[1]Savarirayan R, Irving M, Bacino CA, et al. C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. *N Engl J Med*. 2019;381(1):25-35. doi:10.1056/NEJMoa1813446

Need for Prospective, Standardized Data Collection

Most important variables

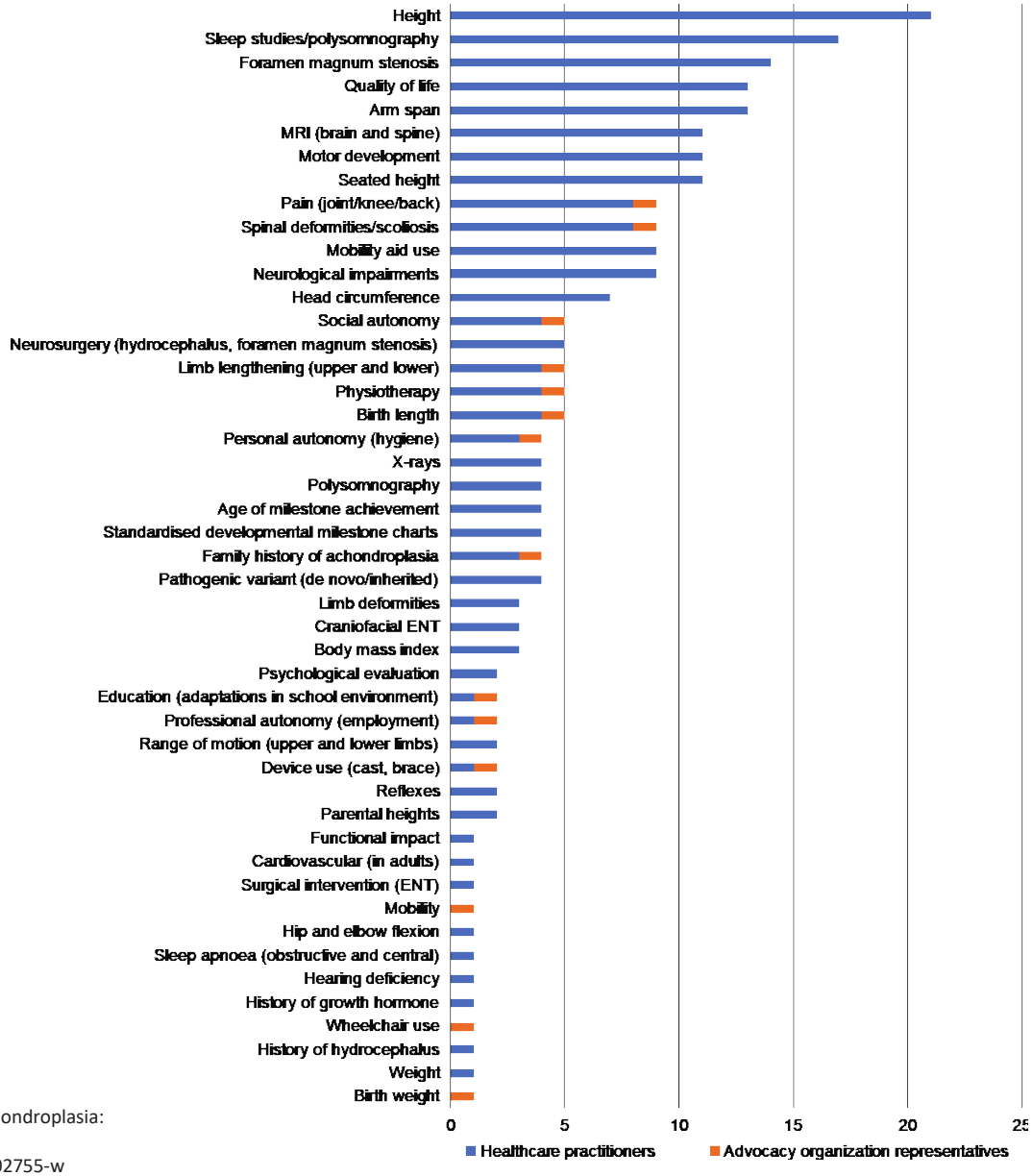


***Figure 1**: Data elements considered of greatest value for an achondroplasia registry*[2]

[2] Alanay Y, Mohnike K, Nilsson O, et al. Real-world evidence in achondroplasia: considerations for a standardized data set. *Orphanet J Rare Dis*. 2023;18(1):166. Published 2023 Jun 26. doi:10.1186/s13023-023-02755-w

The Achondroplasia Module: Design and Current Status

Achondroplasia Module: Design

- Part of EuRREB Core Registry (Since 2022) – *Recently updated*
- **Key study focuses**
  - Children: Thoracolumbar kyphosis, spinal stenosis and foramen magnum stenosis
  - Adults: Thoracolumbar kyphosis and spinal stenosis
- **Longitudinal follow up:** anthropometric data, diagnostics, medical treatment and surgical treatment
- **Patient-Reported Outcome Measures** (PROMs)

Achondroplasia Module: Current status

- **Data from 5 centers**
- **Adult database**
  - 100 patients
  - 77 patients underwent thoracolumbar spine surgery
  - 60 patients filled in PROMs
- **Children database**
  - 39 patients
  - 25 children treated with vosoritide

New Insights: Spinal Pathology in Achondroplasia

New Insights: Spinal Pathology in Achondroplasia

Children

- Thoracolumbar kyphosis (TLK)
- Formed from improper seating posture

Adults

- Spinal stenosis
- Upper lumbar levels

New Insights: Spinal Pathology in Achondroplasia

- Evaluate each vertebral level individually (From Th12 to S1)
- Assess correlation between:
  - Severity of TLK (°)
  - Severity of stenosis (Schizas scale)

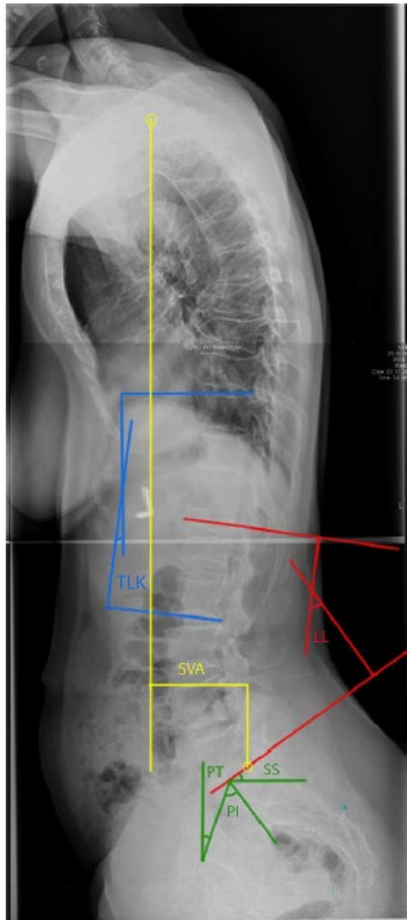


***Figure 3**: Measurement method of sagittal balance parameters* [3]

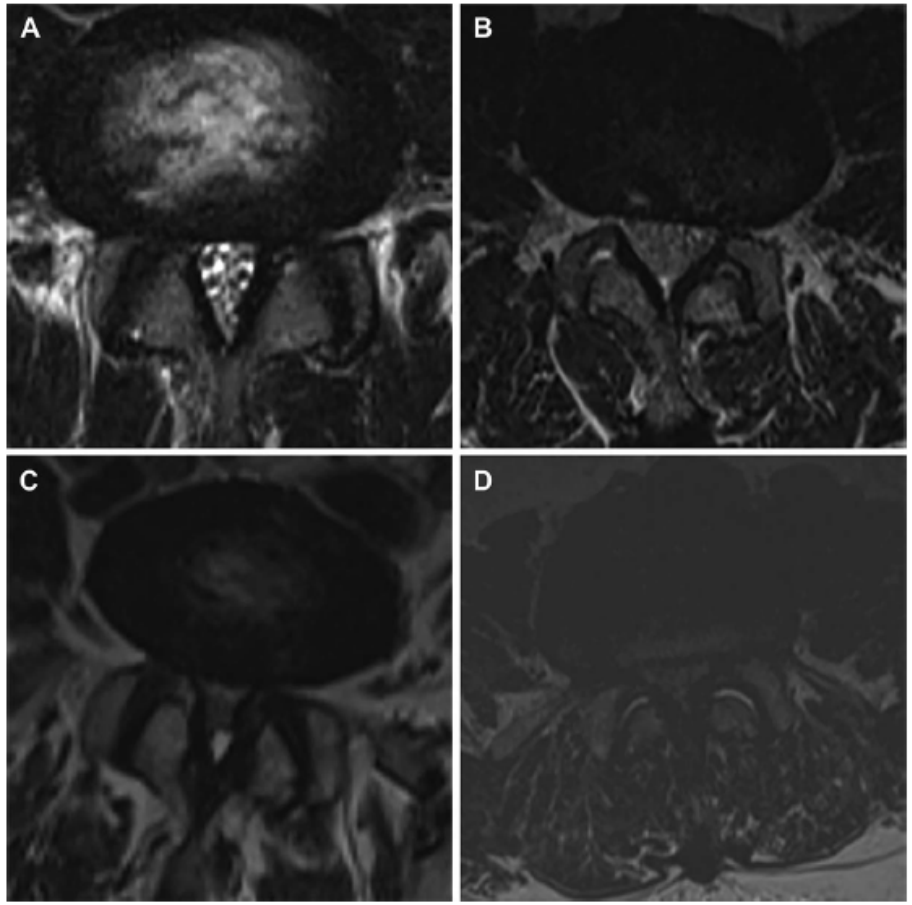


***Figure 4**: Schizas scale overview on axial T2-weighted MRI* [3]

[3] Cai H, Omara C, Vleggeert-Lankamp CLA. Association Between Radiological Severity of Lumbar Spinal Stenosis and Spinopelvic Parameters in Adult Patients With Achondroplasia. *Neurosurgery*. 2024;95(6):1317-1328. doi:10.1227/neu.0000000000003007

New Insights: Spinal Pathology in Achondroplasia

TABLE 4. Correlation Between Schizas Scales and Sagittal Balance Parameters

	Schizas scales					
	T12L1	L12	L23	L34	L45	L5S1
TLK						
r (p)	0.10 (0.727)	0.44 (0.020)[a]	0.29 (0.121)	0.14 (0.457)	−0.26 (0.150)	0.07 (0.728
N	14	29	30	33	34	31

- **Positive correlation** between the presence of **TLK** and **upper lumbar spinal stenosis** (r=0.44, *p=0.020*)
- Multivariate linear regression: Every **1 degree** increase in **TLK → 1% worse** outcome on **EQ-5D**

[3] Cai H, Omara C, Vleggeert-Lankamp CLA. Association Between Radiological Severity of Lumbar Spinal Stenosis and Spinopelvic Parameters in Adult Patients With Achondroplasia. *Neurosurgery*. 2024;95(6):1317-1328. doi:10.1227/neu.0000000000003007

New Insights: Spinal Pathology in Achondroplasia

Children

Adults

Which patients are at risk for developing persistent TLK?

New Insights: Spinal Pathology in Achondroplasia

- **Meta-analysis** on **risk factors** for persistent **TLK** in children with achondroplasia
- Significant clinical parameters
  - Developmental motor delay (OR 3.0; 95% CI 1.5 – 5.9; p = 0.002)
- Significant radiological parameters
  - Percentage vertebral wedging (MD 10.9%; 95% CI 5.6% – 16.3%; $p < 0.001$),
  - Apical vertebral translation (OR 8.4; 95% CI 2.8 – 25.4; $p < 0.001$)

New Insights: Spinal Pathology in Achondroplasia

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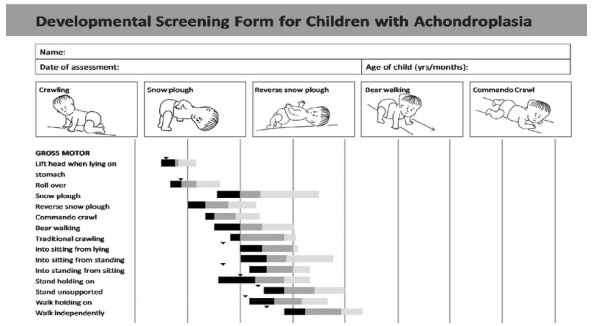

New Insights: Spinal Pathology in Achondroplasia

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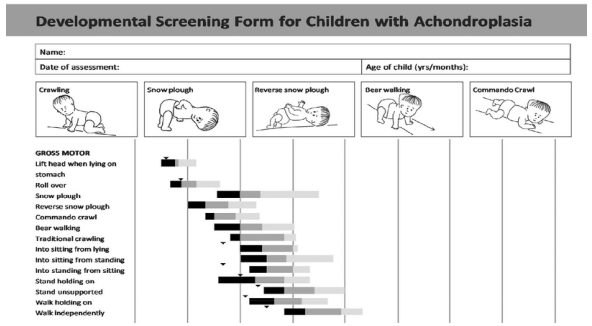
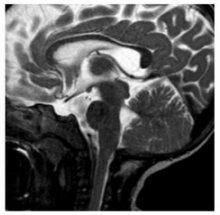
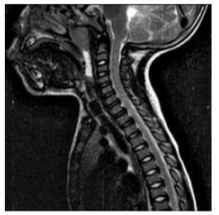
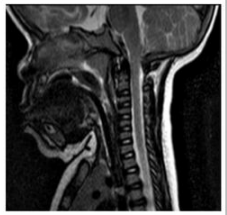
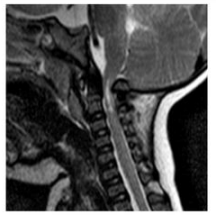
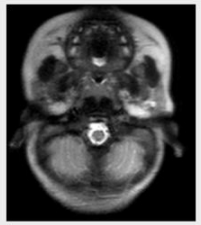
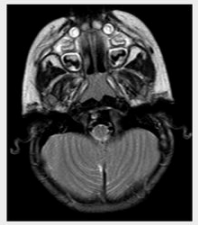
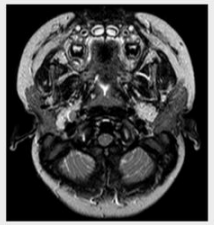
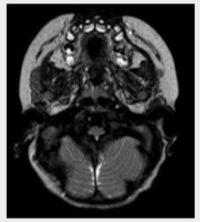
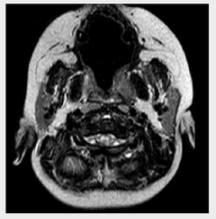


Optimal management requires a coordinated multidisciplinary approach

Next Steps and Research Directions

Next Steps and Research Directions

- Continue research on spinal pathology in achondroplasia
- Optimal management of foramen magnum stenosis
  - Wide variation across centers: MRI vs clinical exam vs polysomnography
  - Some centers operate early, others only if symptomatic

AFMS0	AFMS1	AFMS2	AFMS3	AFMS4
Normal foramen magnum	Constitutional narrowing of the foramen magnum with preserved CSF (no cord distortion)	Narrowing of the foramen magnum with loss of CSF space surrounding the cord	Loss of the CSF space with cord compression	Cord compression and signal changes (Myelomalacia)
				
				

Call for collaboration

- Join the achondroplasia module!
- Multidisciplinary participation is essential

- Need help?

Achondroplasia Working group

Achondroplasia

Members of this Working Group

Lead: Klaus Mohnike	pediatric endocrinologist
Co-Lead: Inês Alves	patient representative, ePAG ERN BOND
Chady Omara	phD candidate, neurosurgeon, responsible researcher
Carmen Vleggeert-Lankamp	neurosurgeon
Geert Mortier	clinical geneticist
Genevieve Baujat	clinical geneticist
Marco Sessa	patient representative
Maria Francesca Bedeschi	clinical geneticist
Mariya Cherenko	endocrinologist, EuRREB data manager
Natasha Appelman-Dijkstra	endocrinologist, EuRREB coordinator
Svein O. Fredwall	senior medical consultant

Achondroplasia Research group
Dept. Neurosurgery, LUMC

Prof. dr. C.L.A. Vleggeert-Lankamp

Dr. H. Cai

Thank you

Ways to contact us:

eurreb.eu

registries@lumc.nl

drop-in sessions via Zoom

European Registries for Rare Endocrine and Bone Conditions

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Endo-ERN
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