Delayed bone formation partly explains tibial anterolateral bowing associated with neurofibromatosis type 1

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Introduction

- Anterolateral bowing of tibia is observed at birth within 4% of the children diagnosed with neurofibromatosis type 1 (NF-1) [1].
- Tibial bowing could further increase with growth, leading to spontaneous fracture (Fig 1), nonunion, and amputation in severe cases.
- NF-1 has been shown to influence cellular interactions involved in angiogenesis and bone formation.

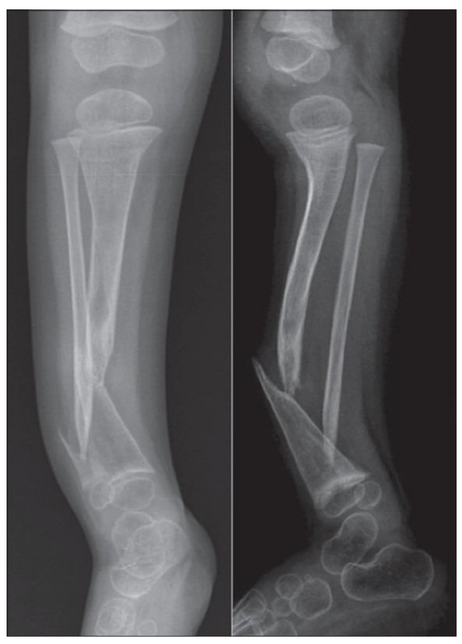

Fig 1) Tibia spontaneous fracture due to NF 1 related excessive bowing [1]

Objective

The objective of this study was to develop a valid mechanobiological model of early long bone growth to investigate the role of NF-1 relevant delayed bone formation in tibial anterolateral bowing at birth.

Methodology

Initial geometry and loading conditions

- An initial geometry mimicking anlage of the condensed mesenchymal stem cells was first considered.
- Dynamic mechanical loads representing contact pressure at the medial/lateral plateaus were applied to the growing model (Fig 2) from embryonic day 90 onwards [2].

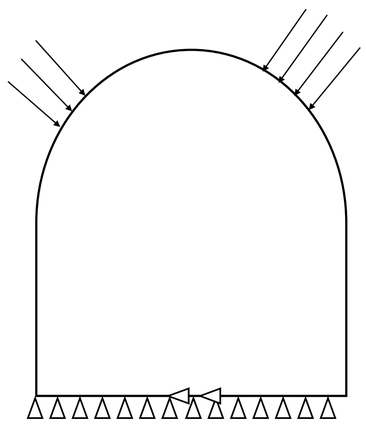

Fig 2) Initial anlage geometry with applied loading and boundary conditions

Growth

- longitudinal growth of long bones is fueled by progressive proliferation and hypertrophy of differentiated chondrocytes which are regulated through interaction between parathyroid hormone related peptide (PHRP) and Indian Hedgehog (Ihh) (Fig 3) whose spatiotemporal variation are governed by reaction-diffusion equation (eq. 1).

$$\frac{DS_i}{Dt} + v_f.\nabla S_i + S_i\nabla.v_g = D_i\nabla^2 S_i + b_i \quad (1)$$

- source terms, b_i, were represented by Schnakenberg equation [2, 3]:

$$b_{PHRP} = C_{pc}\left(\alpha_1 - \beta_1 S_{PHRP} + \gamma_1 S_{PHRP}^2 S_{Ihh}\right) \quad (2)$$

$$b_{Ihh} = C_{pc}\left(\alpha_2 - \gamma_1 S_{PHRP}^2 S_{Ihh}\right) \quad (3)$$

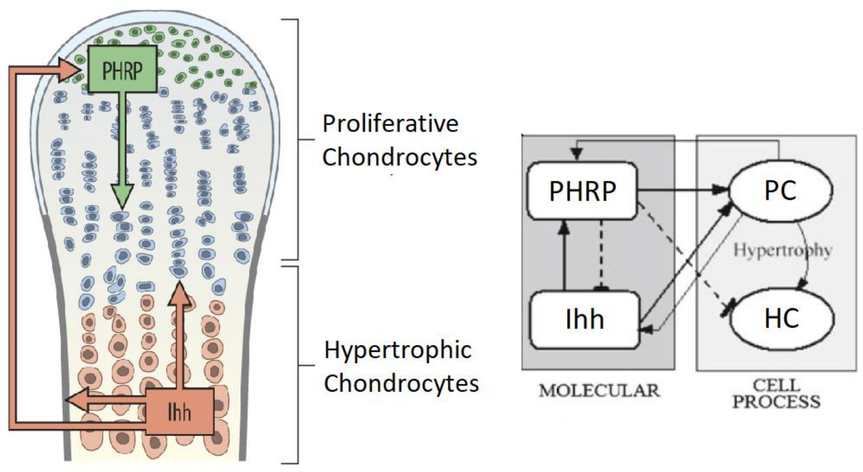

Fig 3) Negative feedback loop between PHRP and Ihh [3]

- v_g represents growth velocity vector, obtained considering proliferation rate of chondrocytes and the enlargement rate of hypertrophic chondrocytes, γ [4]:

$$\gamma(t) = \alpha_{mech}\frac{t^{\beta-1}e^{-t/\theta}}{K} \quad (4)$$

in which t is the time elapsed since hypertrophy has started and $\alpha_{mech}$is a dimensionless factor, between 0.75 to 1.25, depending on the mechanical stress [4].

- v_f represents interstitial fluid velocity and was obtained by solving equations of poroelasticity:

$$\nabla.\tau = 0 \quad (5)$$

$$\nabla.\dot{u} - \nabla.\left(\frac{k}{\rho g}\nabla P\right) = 0 \quad (6)$$

in which τ is stress tensor, u is displacement vector, P is pressure, k is coefficient of permeability, ρ is density, and g is gravity constant.

- Angiogenesis is enhanced via VEGF production by hypertrophic chondrocytes whose spatiotemporal distribution obeys eq. 1 with the source term, b_{VEGF}, as [2]:

$$b_{VEGF} = r s_{VEGF}\, C_{hc}\left(1 - \frac{s_{VEGF}}{P_{VEGF}}\right) + \chi_{VEGF} C_{hc} \quad (7)$$

- Bone formation was assumed to occur when a certain threshold of VEGF concentration is reached.

Analysis

- The constants in eqs. 1 to 7 were adopted from literature [1-4].
- The system of eqs. 1 to 7 were solved using finite element method in the FreeFEM++ environment.

Results

- Predictions of spatial arrangement of proliferative chondrocytes (Fig 4) fit well with physiological observations of the growing tibia [3].
- Our results revealed increased bowing at birth with higher thresholds of VEGF (Fig 5).

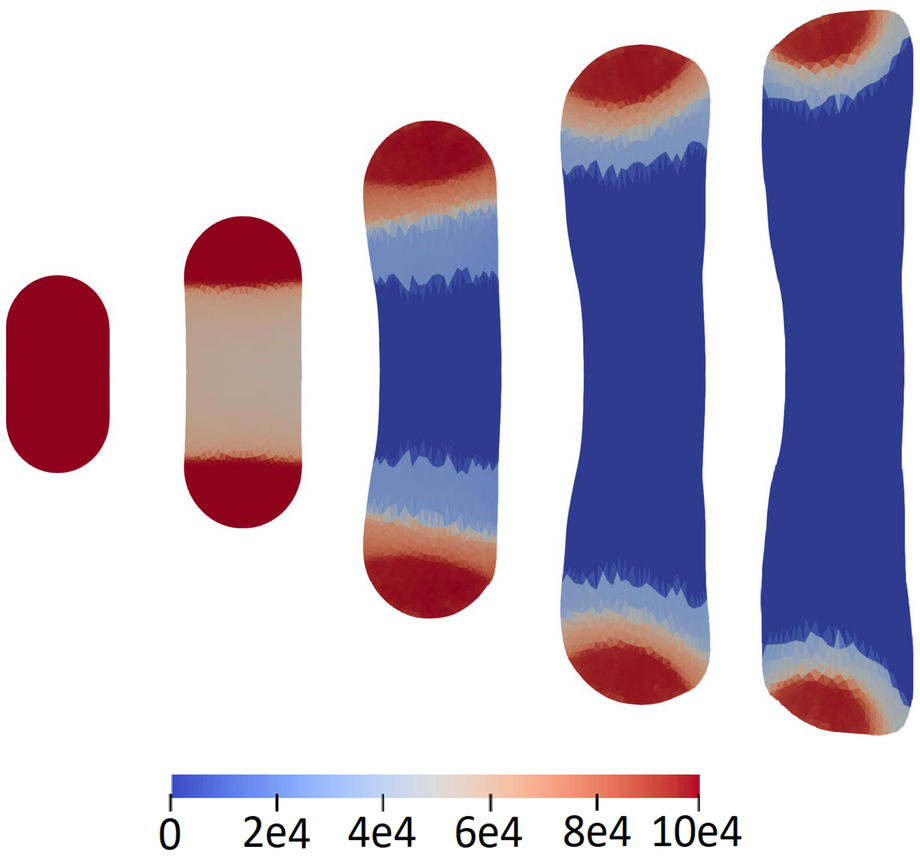

Fig 4) Distribution pattern of proliferative chondrocytes from embryonic day 50 to 270

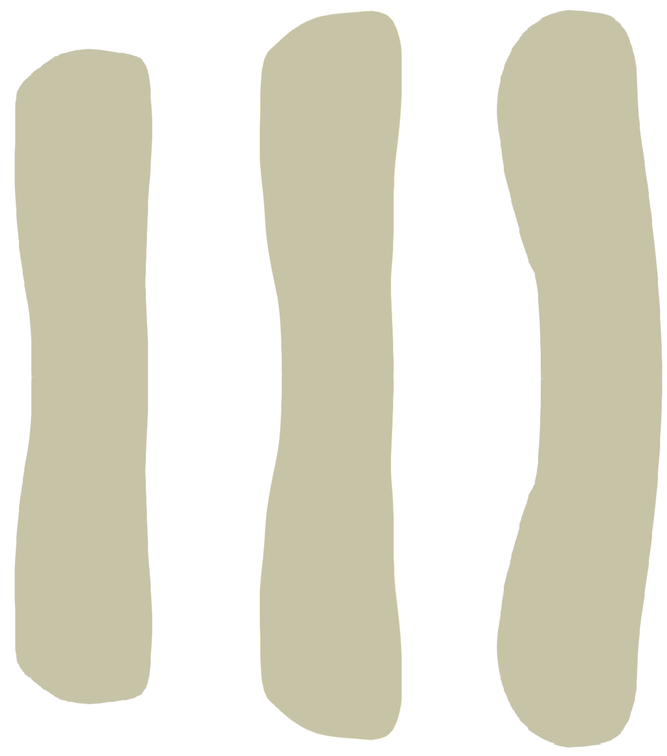

Fig 5) Predicted morphology of the tibial bone at birth for VEGF concentration of 0.027, 0.030, and 0.033 ng/mm (from left to right).

Conclusion

NF-1 related delayed bone formation may explain anterolateral bowing of tibia at birth.

References

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