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A mutant mouse model of Hajdu-Cheney syndrome

Canalis E
UConn Health, USA

Hajdu-Cheney syndrome (HCS) is a rare but devastating genetic disease characterized by craniofacial developmental abnormalities, acro-osteolysis, severe osteoporosis with fractures and sudden death. HCS is associated with a gain-of-function of *NOTCH2*, where point mutations in exon 34 lead to a truncated and stable *NOTCH2* protein product. To study and understand HCS, we created a mouse model harboring a *Notch2* mutant allele reproducing the mutation found in subjects with HCS. The 6955C>T mutation in mice created a stop codon at glutamic acid 2319, upstream the PEST domain which is required for Notch degradation. Sequences necessary for *Notch2* transcriptional activity are preserved. The 6955C>T mutation was introduced into the *Notch2* locus by homologous recombination, verified by DNA sequencing and mice characterized following removal of the selection cassette. Notch target genes were induced in tissues of *HCS-Notch2* mice, demonstrating Notch signal activation. Homozygous *HCS-Notch2* mutants exhibited newborn lethality, whereas heterozygous mice had pronounced bone loss. Micro-computed tomography of *HCS-Notch2* mutants revealed a 50-55% decrease in cancellous bone volume and markedly decreased connectivity. Cortical thickness, total and cortical cross-sectional areas were decreased by 20-40%. Histomorphometry revealed increased osteoclast number and bone resorption and only a modest decrease in bone formation. Bone marrow mononuclear cells had an increased capacity to form multinucleated osteoclastsin response to M-CSF and RANK-L, explaining the enhanced bone resorption. Osteoblast cultures exhibited increased RANK-L mRNA. In conclusion, a genetically engineered *HCS* mutant mouse model recreates the human disease and exhibits pronounced osteopenia due to an increased osteoclastogenesis and bone resorption. For the first time, the skeletal pathogenesis of HCS is explained.

canalis@uchc.edu

FVC deterioration, airway obstruction determination and life span in Ataxia telangiectasia

Daphna Vilozni
Tel-Aviv University, Israel

Rationale: Forced vital capacity (FVC) values decrease with progress of the disease in Ataxia telangiectasia (AT).

Objective: To study the effect of this process on airway obstruction determination and life span in AT.

Methods: Clinical data and yearly best spirometry maneuvers were collected retrospectively from 37 AT patients (196 spirometry tests) during 5.4±1.8 years (initial age 4-21 years). Twelve patients were walking (7 of them had recurrent respiratory system infections); 25 subjects were confined to wheelchair, of them 8 patients were towards end-stage lung disease. Spirometry indices included Forced Vital Capacity (FVC), mid-expiratory-flow (FEF25-75) and tidal volume (VT). We calculated FEF25-75/FVC and VT/FVC ratios.

Results: FVC declined from 67±8 while walking to 19±6% predicted values. FEF25-75 values that were elevated (116±23% predicted) while walking, decreased to 69±27% predicted at end-stage where 7 patients responded to bronchodilators. VT/FVC ratio was 0.25±0.06 while walking, increased to 0.35 once on wheelchairs and further increased to 0.57±0.19 at end-stage disease. FEF25-75/FVC ratio was 2.54±0.70 above normal (~1.0) increasing to 4.16±0.75 at end stage. A sharp elevation was seen in FEF25-75/FVC ratio when FEV1 was still ~45 % predicted and 2-years prior to death.

Conclusions: Having a low baseline-FVC (60% predicted) artificially raises FEF25-75 values, so FEF25-75 of "mild obstruction" values may indicate severe airway obstruction in AT subjects. VT/FVC and FEF25-75/FVC ratios may therefore assist in revealing higher than normal breathing effort. The results further suggest adding VT/FVC and FEF25-75/FVC ratios to pulmonary function assessments in patients with AT.

avi_vil@bezeqint.net