

IMPACT OF INFANCY LENGTH ON CHILD GROWTH IN 22 SUBSISTENCE-BASED SOCIETIES

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Context: Humans evolved to withstand energy crises by a predictive adaptive response, decreasing their body size. Thus, short-term adaptations to energy crises defer the infancy-childhood transition age (ICT), culminating in short stature. In natural-fertility human societies, this transition is associated with weaning from breastfeeding and the mother's new pregnancy. We therefore used the inter-birth interval (IBI) as a surrogate for the ICT. **SAMPLE:** The sample used is 22 natural-fertility societies of foragers, horticulturalists and pastorals from Africa, South America, Australia and Southeast Asia.

Hypothesis: We hypothesized that late ICT would be associated with smaller adult size and predicted that the IBI will negatively correlate with body size.

Results: The IBI (range 28.6-45.1 mo) correlated negatively with average adult bodyweight for females $r=-.537$, $p=.012$, and males, $r=-.475$, $p=.025$ and with adult BMI for females ($r=-.467$, $p=.033$) but not for males ($r=-.387$, $p=.075$). IBI correlated negatively with 1-year old bodyweight and with gestation to one year weight gain for males ($r=-.678$, $p=.015$; $r=-.694$, $p=.018$, respectively) but not for females ($r=-.473$, $p=.088$; $r=-.473$, $p=.088$, respectively), and positively with the age 3 mass as % of adult mass for both females ($r=.695$, $p=.008$) and males ($r=.662$, $p=.014$, fig 2). Juvenility and adolescent growth variables did not correlate with the IBI. *IBI correlated negatively with population density ($r=-.526$, $p=.044$). For males, less so for females, BMI correlated negatively with population density ($r=-0.636$, $p=.011$; $r=-.512$, $p=.051$, respectively3). When categorizing societies by economy-type, the IBI was longest in foragers, with a mean 38 mo, and shortest in mixed peasant economies with a mean IBI of 28 mo, $p < 0.001$.*

Conclusions: This inter-population study of natural-fertility human societies shows population density to correlate negatively with BMI, and adult size to be adaptively smaller when BMI is low. The mechanism for this adaptation utilizes the trade-off of infancy length against adult size, supporting the ICT theory, of negative relation between the ICT age and adult height.

EMPIRICAL TESTING OF THE 'INFANCY – CHILHOOD TRANSITION (ICT) THEORY' ON GROWTH REGULATION

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Introduction: The ICT theory on child growth claims a central role for the age at ICT in determination of growth pattern and ultimate adult height, such that delayed ICT (DICT) results in short stature, and early ICT – tall stature. The theory has been proven by multiple human observations. To empirically test the theory in experimental animals the ICT was assumed to be controlled by weaning from lactation.

Hypothesis: Early weaned animals will be longer than late weaned.

Methods: Sprague-Dawley pups, which usually are weaned at age 21 days, were weaned by transfer to foster non-lactating mothers at age 16, 21 or 26 days, and separated from these mothers at age 30 day. Growth was followed at weekly intervals until age 90 days.

Results: Early weaning animals (day 16) grew faster as of day 30 to reach a 60 day length of 41.90 ± 0.49 cm and 90 days length of 44.19 ± 0.75 , as compared to late weaning rats (26 days) with lengths of 35.68 ± 1.54 ($p < 0.001$) and 38.65 ± 1.9 ($p < 0.001$), respectively.

Weights of the early weaning rats were 362.5 ± 38.28 and 428.56 ± 31.56 at 60 and 90 days, as compared to 281.5 ± 21.53 ($p < 0.001$) and 365.13 ± 19.61 ($p < 0.001$), respectively, in the late weaning animals.

On the other hand the BMI grew smaller by early weaning. BMIs of the early weaning rats were 0.206 ± 0.02 and 0.219 ± 0.01 at 60 and 90 days, as compared to 0.222 ± 0.02 ($p < 0.05$) and 0.245 ± 0.01 ($p < 0.05$), respectively, in the late weaning animals.

Conclusions: Delayed (DICT) as compared to early ICT results in shorter and heavier animals. The ICT theory, as developed by human observations, is supported to be valid in experimental rats. Weaning may control the ICT.

THE LENGTH OF INFANCY CONTROLS INFANTILE AND JUVENILE DEVELOPMENT, AND THIS ADAPTIVE RESPONSE IS TRANSMITTED TRANS-GENERATIONS

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The preadult life history of rats is divided into infancy, as defined by lactation, and juvenility to reach in the female vaginal opening at a mean age of 35 days, whereas in the male, testes reach adult size of 2.3 ml mean age 37 day (day 21 F1).

Hypothesis: The length of infancy controls infantile and juvenile development, and this adaptive response is transmitted trans-generations.

Methods: Sprague-Dawley pups (generation F1), which usually are weaned at age 21 days, were weaned by transfer to foster non-lactating mothers at age 16, 21 or 26 days, and separated from these mothers at age 30 day. At age 60 females and males were mated within the weaning groups and generation F2 pups were followed for their infantile and juvenile developmental milestones.

Results: Generation F2 pups shifted their infantile developmental milestones such that males pups of early weaning parents (day 16) had earlier fur development at age 8.7 ± 0.67 as compared to 10.38 ± 1.6 in pups of late weaning parents (26 days) ($p < 0.05$). pinnae detachment was also earlier in d16 F2 (10.7 ± 0.82) as compared to 13.13 ± 0.64 in d26 F2 ($p < 0.05$). Eye opening occurred at day 15.7 ± 0.48 in d16 F2, as compared to 16.38 ± 0.52 ($p < 0.05$) in d26 F2.

Generation F2 pups shifted their infantile developmental milestones such that females pups of early weaning parents (day 16) had earlier fur development at age 8 ± 0.53 as compared to 10.75 ± 0.71 in pups of late weaning parents (26 days) ($p < 0.05$). pinnae detachment was also earlier in d16 F2 (10.63 ± 0.74) as compared to 13.38 ± 0.52 in d26 F2 ($p < 0.05$). Eye opening occurred at day 15.5 ± 0.53 in d16 F2, as compared to 16.25 ± 0.46 ($p < 0.05$) in d26 F2.

Conclusions: The age at weaning programs life history adaptively, to be transmitted trans-generation. Shorter infancy results in a trans-generational shift to earlier infantile and juvenile development.

AUTOSOMAL RECESSIVE HYPONATREMIA DUE TO ISOLATED SALT WASTING IN SWEAT ASSOCIATED WITH A MUTATION IN THE ACTIVE SITE OF CARBONIC ANHYDRASE 12

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Introduction: Genetic disorders of excessive salt loss from sweat glands have been observed in pseudohypoaldosteronism type I (PHA) and cystic fibrosis that result from mutations in genes encoding epithelial Na⁺ channel (ENaC) subunits and the transmembrane conductance regulator (CFTR), respectively. We identified a novel autosomal recessive form of isolated salt wasting in sweat which leads to severe infantile hyponatremic dehydration.

Results: Three affected individuals from a small Bedouin clan presented with failure to thrive, hyponatremic dehydration, and hyperkalaemia with isolated sweat salt wasting. Linkage analysis and genes sequencing ruled out an association to the CFTR and ENaC genes. Using positional cloning we identified an association of a Glu143Lys gene mutation in *carbonic anhydrase 12* (CA12) with the disease.

Conclusion: Carbonic anhydrase is a zinc metalloenzyme that catalyzes the reversible hydration of carbon dioxide to form a bicarbonate anion and a proton. Glu143 in CA12 is essential for zinc coordination in this metalloenzyme and lowering of the protein-metal affinity reduces its catalytic activity. This is the first presentation of an isolated loss of salt from sweat gland mimicking PHA, associated with a mutation in the CA12 gene not previously implicated in human disorders. Our data demonstrate the importance of bicarbonate anion and proton production on salt concentration in sweat and its significance for sodium homeostasis.

A NOVEL C-TERMINAL FSH β MUTATION CAUSE PRIMARY AMENORRHEA IN THREE SIBLINGS

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Context: Inactivating mutations of the FSH β subunit gene, causing isolated FSH deficiency and hypogonadism are very rare autosomal recessive disorder. To date, only six women with delayed puberty and isolated FSH deficiency have been reported worldwide.

Objective: Clinical and molecular studies in three Palestinian sisters with impaired pubertal development and primary amenorrhea.

Patients and Methods: A 15y old female presented with delayed puberty (breast tanner II, pubic hair tanner IV), primary amenorrhea, and undetected basal serum FSH. LH peak during LHRH test was extremely high at 135mIU/ml while FSH remained low at <0.1mIU/ml. Abdominal sonography showed an infantile uterus. Two additional sisters presented later with a similar phenotype. Full pubertal development and menarche were easily achieved by estrogen and later progesterone replacement therapy. DNA was extracted from peripheral leukocytes and sequenced for FSH beta gene.

Results: A homozygous 1base pair frameshift deletion mutation in exon3 (**354delGfs9**) of the FSH β gene was found in all three affected patients predicting an alteration of the 9 amino acids following codon 118 and a premature stop codon at position 127. The parents and two healthy sisters were heterozygous for this deletion mutation.

Conclusions: A novel FSH β mutation has been detected in three hypogonadal sisters. This is only the fifth FSH β mutation reported world wide and the first mutation not involving the cystine knot and the three β hairpins of the protein that are essential to hormone binding. Further studies are required to determine the crucial role of the c-terminal 11 amino acids of FSH β on the function of FSH given the severe clinical phenotype observed in our patients.

SEXUAL INTERESTS AND HYPOGONADISM IN PRADER-WILLI SYNDROME (PWS)

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Background: Hypogonadism is a major feature of Prader-Willi syndrome, but clinical manifestations are variable. Sexual interests and behavior in this population have not been previously described.

Objectives: We studied PWS adolescents and young adults to assess (1) satisfaction with physical and sexual development (2) frequency of romantic and sexual experiences, (3) aspirations and expectations regarding marriage, (4) investigate the relation between sexual interests and hormone levels, and (5) assess the desire for hormonal replacement therapy.

Methods: The study population consisted of 27 individuals (13 males) ages 17 to 32 (mean 23.5) years with genetically confirmed PWS. Mean IQ was 75 (range 50 – 100). We conducted structured interviews using questionnaires specifically designed for this study.

Results: There was a significant negative correlation between IQ and body image in both males and females. IQ showed a positive correlation with interest in dating and romantic activities. Approximately half of PWS males and females reported having gone on a date and kissing romantically. All males and 64% of the females wished to be married. Seventy-seven percent of PWS males wanted hormonal treatment to increase phallic size. We found no correlation between hormone levels and sexual interests. Only 43% of PWS females wanted hormonal medication to achieve regular menstruation.

Conclusions: Despite documented hypogonadism, PWS young adults are interested in sexual and romantic issues. The range of sexual activities and expectations is variable. Understanding specific sexual characteristics of each individual is important in order to offer proper anticipatory sexual guidance counseling and for appropriate recommendations for hormone replacement.

LACK OF ASSOCIATION BETWEEN SEROCONVERSION AND CATCH-UP GROWTH IN CHILDREN WITH CELIAC DISEASE

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Objective: To assess the association between seroconversion and catch-up growth during the first year of gluten-free diet (GFD) in children with celiac disease (CD).

Study design: Medical records of all biopsy-proven CD children diagnosed between January 1999 and August 2009 were reviewed, and only prepubertal patients were included. Growth parameters and celiac antibodies were documented before initiation of GFD, after 6 months (period 1) in 55 patients (21 males, age 0.9-12.2 y), and after 12 months (period 2) in 37 patients of the original cohort. All growth data were transferred to standard deviation scores (SDS).

Results: Mean height velocity SDS was significantly higher in period 1 compared with period 2 (2.90 ± 3.20 vs. 0.20 ± 2.08 , $p < 0.001$) irrespective of the serological status of the patients, while the difference in mean weight-SDS gain approached a statistical significance (0.47 ± 0.82 vs. 0.15 ± 0.38 , $p = 0.074$). Mean height-SDS and mean weight SDS levels after 6 months of gluten withdrawal were significantly higher than corresponding baseline levels both in seropositive patients (-0.47 ± 0.91 vs. -0.82 ± 0.82 , $p < 0.001$ and -0.59 ± 1.17 vs. -1.11 ± 1.33 , $p < 0.001$, respectively) and seronegative patients (-1.02 ± 1.14 vs. -1.50 ± 1.12 , $p < 0.001$ and -1.19 ± 1.27 vs. -1.45 ± 1.40 , $p = 0.048$, respectively). Similarly, these growth parameters were significantly higher at the end of period 2 compared with the beginning of that period, but only in seropositive patients: -0.43 ± 0.97 vs. -0.53 ± 0.91 , $p = 0.029$ and -0.53 ± 0.86 vs. -0.75 ± 0.88 , $p = 0.009$ for height-SDS and weight-SDS, respectively. Mean levels of height velocity SDS, and the gain of weight-SDS, BMI and BMI-SDS were similar in the seropositive and seronegative groups, in both periods of the study.

Conclusions: The most remarkable catch-up growth in children with CD is expected during the first 6 months of GFD, irrespective of the serology status.