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GROWTH IN A GIRL WITH NESIDIOLASTOSIS DURING AND AFTER TREATMENT WITH THE SOMATOSTATIN ANALOGUE: SMS 201-995.

Severe hyperinsulinism can be treated with somatostatin analogues. We studied growth and growth hormone(gh) in a patient with nesidioblastosis, treated with SMS 201-995. In a Moroccan female with nesidioblastosis subtotal pancreatectomy was performed at an age of 4 weeks. Because of recurrent hypoglycaemia SMS 201-995 was instituted from an age of 11 months till 3.1 yrs. In a dose of 8 x 25 µg/day s.c. SMS 201-995 resulted in normoglycaemia (portable infusion pump, Ferring). The SMS treatment could be ceased at an age of 3.1 yrs. Growth velocity during the last 6 months of treatment was 5.2 cm/yr. In the year after discontinuation of therapy growth vel. increased to 12.2 cm yr. (CA:4.0 yr). During treatment SMC level was normal to slightly elevated (162 ng/mL); maximum gh level during sleep decreased with the treatment period and was 8.2 µg/L. just before discontinuation. 14 days off treatment max. gh had increased to 13 µg/L.

Conclusion: Chronic subcutaneous therapy (2.2 yrs) of SMS 201-995 was successful in preventing hypoglycaemic periods in a girl with nesidioblastosis. Growth hormone secretion was gradually impaired during treatment. Catch up growth after discontinuation of therapy makes evident that growth was impaired during treatment with the somatostatin analogue SMS 201-995.

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PROGRESSIVE ENCEPHALOPATHY IN PATIENT TREATED WITH PITUITARY HUMAN GROWTH HORMONE

We report the case of a hypopituitary patient treated with human pituitary-derived growth hormone with a neurological disorder initially thought to be Creutzfeldt-Jacob disease (CJD). Between 1978. and 1981. he received 150 injections of Kabi-Vitrum Creshormone. In 1985. at the age of 18 he began to have difficulty in speech, writing and balance and exhibited behaviour changes. CT scan of the brain revealed massive calcifications within cerebellar hemispheres. Other laboratory results including cerebrospinal fluid (CSF) analysis, serum electrolytes and parathormone levels and EEG were normal. His father's CT scan of the brain showed a minor calcification of the caudate nucleus, without clinical symptomatology. Follow-up of the patient revealed slow but clear progression of speech, truncal and gait ataxia and coordination difficulties. He became withdrawn, depressive and slightly aggressive. Repeated EEGs were normal and the pair of proteins characteristic for CJD were not detected in CSF. Most probably our patient has Fahr's disease (familial basal ganglia calcification) but for a definitive diagnosis histopathology of the brain would be needed.

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ACUTE LYMPHOCYTIC LEUKEMIA IN A PATIENT ON GROWTH HORMONE (GH) TREATMENT

With the availability of rDNA-GH, GH is applied in experimental trials to other groups of patients than with GH-deficiency. Most effects of GH and GH-factors are clear; an effect of malignant degeneration is unknown.

Patient. In a 12.3 yrs old girl with idiopathic GH-deficiency pit-GH was instituted with 2 x 4 IU/wk/im (12.7 IU/m<sup>2</sup>/wk) at 5.5 yrs. At 6.6 yrs a pericarditis of unknown origin developed; pericardectomy was necessary. At 9.7 yrs GH treatment was stopped and resumed at 10.3 yrs with rDNA-GH 6 x 2 IU/wk/sc (12 IU/m<sup>2</sup>/wk). Throughout GH treatment growth was satisfactory.

At 11.2 yrs she had muscle weakness resulting in failure to walk. Neurological, (including muscle biopsy) and laboratory investigation did not reveal abnormalities. Prednisone improved the weakness temporarily. She developed anaemia and hepatosplenomegaly and on examination of blood and bone marrow a diagnosis of a CALLA-positive acute lymphocytic leukemia was made. The leukemic cells did not show chromosomal aberrations. Cytotoxic treatment resulted in complete remission and disappearance of the muscle weakness.

Conclusion. A 12.3 yrs old girl developed common ALL, while on GH treatment. No causal relationship could be proven. However, this case is reason to stress the necessity of strict indications for GH treatment.

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IGF-1 AND IMPAIRED GROWTH IN CROHN'S DISEASE

Growth retardation in juvenile patients with Crohn's disease usually is only diagnosed retrospectively by growth rate measurements. However, on time therapy requires early detection. Other authors have claimed that serial IGF-1 measurements may be a useful marker of reversibility of impaired growth in children with chronic inflammatory bowel disease. In order to evaluate parameters useful to predict growth retardation we followed 26 juvenile patients by estimation of growth velocity, weight gain, Best activity index (AI) and serum levels of α-1-glycoprotein (GP), albumin and IGF-1 over periods of 6-12 months. RIA-IGF-1 was measured in serum after acid-ethanol extraction using an antiserum supplied by the NHPP, Baltimore, Md.

Age corrected IGF-1 levels at the end of, but not before an observation period of 6 months were correlated to growth velocity (r= 0.57; p<0.01) and weight gain (r= 0.44; p<0.05). % weight gain also was correlated to % change of IGF-1 levels (r= 0.50; p<0.01). In contrast, there was no relation of IGF-1 to AI, GP and albumin levels, which again did not correlate to clinical parameters of growth.

In conclusion: IGF-1 appears to be a better index of growth retardation compared to other parameters tested, but its value for the long-term follow-up of patients with chronic inflammatory bowel disease is limited.

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RESTRICTION FRAGMENT LENGTH POLYMORPHISM (RFLP) OF THE INSULIN-LIKE GROWTH FACTOR I (IGF I) GENE IN FRENCH SUBJECTS

Genomic DNA extracted from leukocytes of 18 French subjects of normal stature was analysed by Southern blot. Specific hybridization was done with the EcoRI-Bam HI insert of the h-IGF I cDNA probe (FEBS Lett., 1986, 196:108) (S. A. : 1.5-2. 10<sup>4</sup> cpm/µg) and washing done at 65°C (0.1x SSC, 0.1% SDS). DNA digested with Hind III yielded fragments of 7.7, 6.7, 5.1, 4.3 and 3.5 kb. The 4.3 kb fragment may have been a partial digestion product despite the high concentrations used (4U/µg, overnight). Six of the DNA samples had an additional 5.6 kb fragment showing Hind III RFLP. Another study with Pvu II yielded 7.3, 4.8, 3.7 (partial digest?), 2.7 and 1.4 kb fragments and an additional polymorphic fragment of 5 kb. Polymorphic Pvu II and Hind III sites are linked; the heterozygous pattern appeared in 33% of the samples studied. Normal restriction patterns were seen in the DNA of 6 subjects with growth disorders (Laron's dwarfism, constitutionally short and tall children), where Hind III and Pvu II RFLPs were observed. Analysis with Hind III of 2 Pygmy DNA samples showed normal restriction patterns, without RFLP. No RFLP was found in the IGF I gene of normal French DNA samples when Bam HI (n=10 ; 17.6, 9.8, 7 kb, a minor 1 and 0.7 kb fragments), EcoRI (n=9 ; 7, 6.2, 4.1 and 1 kb) or Taq I (n=8; 10.4, 5, 3.6, 2.5 and 1.6 kb) were used. Taq I digestion of 2 Pygmy DNAs gave normal restriction patterns.

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INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR EXPRESSION ON MITOGEN-STIMULATED LYMPHOCYTES

Isolated human lymphocytes were incubated for 48 hours in FCS/RMPI-1640-medium with the addition of different mitogens (PHA, OKT-3, -4, -8 and PWM). The IGF-1 receptor affinity did not change before and after incubation with these mitogens (1.24+/-0.21 versus 1.41+/-0.68 10<sup>4</sup> M(-1); n=9). For PHA (1 µg/ml) and OKT-3 (25 ng/ml) stimulated lymphocytes we could demonstrate an increase of IGF-1 receptors / cell from 1640+/-350 to 2910+/-870 for PHA (n=7) and from 1770+/-390 to 2780+/-1280 for OKT-3 (n=9). In contrast, B-cells stimulated by PWM (10 µg/ml) did not show any effect on IGF-1-binding. Stimulation of helper- and suppressor T-cells by OKT-4 and OKT-8 also did not influence IGF-1 binding. A dose dependent down regulation of IGF-1 receptor number could be demonstrated by addition of IGF-1 to cultured cells. In contrast to PHA and OKT-3, IGF-1 itself had no effect on DNA- or protein synthesis. Our results support the previous observation that IGF-1 binding to lymphocytes is increased by stimulation of T- but not of B-cells.