

# The Presence of Normal Levels of Serum Immunoreactive Insulin-like Growth Factor 2 (IGF-2) in Patients with Down's Syndrome

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## ABSTRACT

The present study was performed to further investigate the levels of somatomedins in Down's syndrome (DS). The results show that the serum levels of immunoreactive insulin-like growth factor 2 (RIA-IGF-2) in patients with DS is within the normal adult range. No age variation among the patients was observed. Since we earlier reported a deficiency of immunoreactive insulin-like growth factor 1 (IGF-1) in DS patients, present study showing normal RIA-IGF-2 levels suggests a selective deficiency of IGF-1 in DS.

## INTRODUCTION

Down's syndrome (DS) is the most prevalent congenital condition associated with mental retardation. It leads to a multihandicap including growth retardation and development of presenile dementia. Even if the chromosomal abnormality of trisomy 21 is well-defined, very little is known about the mechanisms causing both the mental retardation and growth retardation.

In healthy adults, two types of serum somatomedins (SM) - insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2) - have been identified from serum (10, 11). After birth, both of these somatomedins increase with age, with IGF-1 obtaining adult values between 6-10 years of age (4, 5) and IGF-2 obtaining adult values after the 1st year of life (18). A fetal form of SM has been proposed to exist prior to birth (13). The SMs are suggested to not only regulate bodily growth, but also brain growth (14, 15).

Serum levels of somatomedins in DS patients at different ages have been reported in an earlier study (17). Patients with DS had significantly reduced values of serum IGF-1 like peptides measured with a radioimmunoassay (17). These findings indicated that immunoreactive IGF-1 fails to rise during childhood in DS. The reduced levels of IGF-1 were accompanied with growth retardation in DS patients. With a radioreceptorassay utilizing fetal brain plasma membrane as matrix and somatomedin A as ligand (RRA-

SMA), elevated serum somatomedin values were obtained. This elevation did not appear to be due to interference by binding proteins. The IGF-2 crossreacts in the RRA-SMA (5), suggesting that the DS patients may show a selective elevation in serum IGF-2 levels. The present study of the serum immunoreactive levels of IGF-2 (RIA-IGF-2) was performed to further investigate the somatomedins in DS patients.

## MATERIAL AND METHODS

Thirty patients with DS were studied, 18 of them were children, aged 8 months to 15 years, and 12 were adults, aged 20 to 56 years. These patients belonged, except for two (a boy of 11.5 years of age and a girl of 14.5 years of age), to the same series as presented earlier (17) and the serum samples examined were also the same as in the previous study.

The reference group consisted of 46 healthy adults in the age range 20 to 70 years (3) and 6 healthy newborn (6). Since Zapf et al. 1981 have shown that there is no age dependence of IGF-2 values in healthy individuals older than 1 year of age, all the values of the DS patients older than 1 year of age were compared with the adult values. Between 0 and 20 years a theoretically drawn range ( $\bar{X} \pm 1$  SD) for the IGF-2 levels was used for comparison of the individual DS values (Fig. 1).

A radioimmunoassay for IGF-2, with Sepharose coupled antibodies and pure IGF-2 as ligand has been used (3). The crossreaction of IGF-1 varied between 8 and 10%. Serum samples were extracted by a simplified acid-ethanol (12.5% 2 N HCl/87.5% EtOH, vol/vol) procedure as described by Daughaday et al. (2). In order to allow comparison with the results obtained in the RIA-IGF-2 by Zapf et al. (18), the present results are expressed in ng equivalents of IGF-2 and corrected for the crossreaction of IGF-1. The arbitrary local reference serum used as standard was shown to contain 980 ng IGF-2/ml after correction for its content of IGF-1.

Mean values are expressed as  $\bar{X} \pm$  SD. Student's t-test was used for statistical evaluation.

## RESULTS

The mean RIA-IGF-2 levels for DS patients of different age groups and the results of t-test when mean values were compared to mean levels of normal adults are given in Table 1. No age variation was observed among patients with DS. When the serum values for the patients with DS at each age group were compared to normal adult values no significant difference was observed (Table 1). The concentration of RIA-IGF-2 in serum from the individual DS patients in relation to age is given in Fig. 1. The IGF-2 values from 4 DS patients below 1 year of age (8-12 months) did not differ from the adult DS values. As shown in Fig. 1, three of these four values fell within the theoretically drawn normal IGF-2 range ( $\bar{X} \pm 1$  SD) for children below 1 year of age. There was no significant

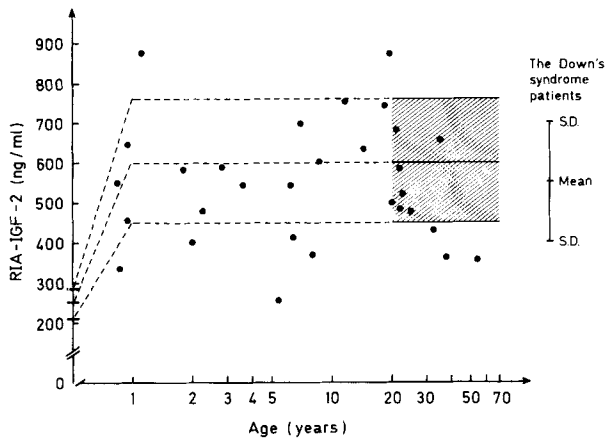


Fig. 1. Serum immunoreactive IGF-2 in relation to age ( $\log_{10}$  years) determined by RIA-IGF-2 (ng/ml) in 30 patients with Down's syndrome (DS). The mean  $\pm$  1 SD for the DS patients is indicated in the right-hand side of the figure. The mean  $\pm$  1 SD for normal adults (20-70 years of age) is shown by the hatched area. The mean  $\pm$  1 SD for cord serum from healthy infants is indicated on the Y-axis. The broken lines indicate the theoretically drawn normal range based on the observation between birth and 20 years of Zapf et al. (1981). Patients with DS: .

correlation between the values of RIA-IGF-2 and earlier published values (17) for immunoreactive IGF-1 (RIA-SMA) ( $r = 0.23$ ;  $p > 0.05$ ), or between the RIA-IGF-2 and RRA-SMA values ( $r = 0.23$ ;  $p > 0.05$ ).

## DISCUSSION

The present results show that the RIA-IGF-2 levels in DS patients are within the normal range. Previously we have reported low levels of serum immunoreactive IGF-1 (17). Thus, similar to pygmies, patients with DS show a selective deficiency of IGF-1 (7). However, in DS the elevation of the serum somatomedins measured with the RRA-SMA method remains to be explained. Since this elevation in RRA-SMA is found after acid exclusion chromatography it cannot be attributed to the interference by binding proteins (17). This assay detects a fetal form of somatomedin, however, IGF-1 and IGF-2 also show crossreaction. From the present results as well as those previously reported, neither IGF-1 nor IGF-2 can account for the elevated RRA-SMA, which instead may be due to a continued presence of the fetal form of somatomedin.

The DS patients thus show a particularly abnormal somatomedin pattern, whose importance in the pathogenesis of the syndrome is unclear. The growth retardation in DS patients (1, 9) may be due to a selective deficiency of IGF-1 like peptides. Since these somatomedins are growth hormone (GH) regulated, the growth retardation in DS

Table 1. Serum mean RIA-IGF-2 levels (ng/ml) ( $\bar{X} \pm 1 \text{ SD}$ ) for different groups of Down's syndrome patients, for cord blood from healthy newborns, and for normal adults, aged 20 to 70 years. The t-values from student's t-test, when compared to normal adults is given; NS = not significant, ( $p > 0.05$ ).

GROUP	Number of individuals	RIA-IGF-2 ( $\bar{X} \pm \text{SD}$ )	t-value compared to adult controls
<u>CONTROLS:</u>			
Adults, aged 20 to 70 years	46	606 $\pm$ 158	
Cord blood	6	242 $\pm$ 36	
<u>DOWN'S SYNDROME:</u>			
<u>Adults</u>			
aged 20 to 56 years	12	556 $\pm$ 156	0.978 NS
<u>Children</u>			
aged 8 to 12 months	4	498 $\pm$ 133	1.323 NS
aged 1 to 15 years	14	553 $\pm$ 164	1.088 NS
<u>Total</u>			
Down's syndrome	30	547 $\pm$ 153	1.610 NS

patients may be explained by suboptimal GH levels. Although normal levels of serum GH have been reported in DS patients (8, 12) and the present findings show normal serum levels of IGF-2, a partial GH deficiency in DS cannot be excluded. The diurnal endogenous production of GH remains to be investigated. The somatomedins are distributed throughout the nervous system (15, 16) where they are proposed to have an anabolic neuroregulatory influence (15). Thus the abnormal somatomedin pattern in DS may not only be of importance for their growth retardation but also for their mental retardation.

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