Dehydroepiandrosterone sulphate (DHEA-S) and corticotropin levels are high in young male patients with conduct disorder:
Comparisons for growth factors, thyroid and gonadal hormones

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SUMMARY

Childhood conduct disorder (CD) may originate in a stressful upbringing, and be associated with unusual physical or sexual development and thyroid dysfunction. We therefore explored circulating levels of hormones from adrenal, gonadal and growth-hormone axes associated with stress, aggression and development in 28 CD patients and 13 age-matched healthy children (10-18 years old). The CD group had higher levels of dehydro-epiandrosterone sulphate (DHEA-S) and corticotropin (ACTH) and free triiodothyronine (fT_3) if under 14 years. There were no differences for gonadal hormones or maturity ratings which were not associated with aggression. Smaller physical measures in CD children correlated with DHEA-S and growth factors (e.g. IGF-I): increased ACTH and fT_3 correlated with restless-impulsive ratings and DHEA-S with 'disruptive behaviour'. Imbalances in the adrenal and growth axes may have neurotrophic repercussions in development.

Key Words: Conduct Disorder,   Dehydroepiandrosterone sulfate (DHEA-S),   Corticotropin (ACTH),   Testosterone,   Thyroid,   IGF-I   Neurodevelopment

INTRODUCTION

Childhood conduct (CD) and oppositional disorders are marked by impulsive verbal and non-verbal aggression [1]. The prevalence and outcome of CD is illustrated by a study of 6,500 males born in Stockholm in 1953; 7.2% had CD problems and 76% of these had a criminal record and/or mental disorder by the age of 30 years [2]. CD predicts the development of personality disorders [3], delinquency and substance abuse [4] and has been related to a dysfunctional family life, low socio-economic status and parental psychopathology [5]. But little attention has been given to endocrinological correlates strongly linked to neural and behavioural development.

Hence we made an exploratory analysis of the function of four hormonal axes associated with stress and development (pituitary-adrenal, gonadal, thyroid and growth) in normal children and those with CD. Pituitary-adrenal function (corticotropin, ACTH; cortisol, CS; dehydroepiandrosterone sulphate, DHEA-S) was studied because of the potential association of stress with the origin of the condition, evidence for disturbed feedback control of pituitary hormones in childhood psychiatric conditions [6] and conflicting reports of CS differences in some CD subgroups [7,8]. Androgens (testosterone, Te; DHEA-S) and oestradiol (E_2) were selected in view of reported associations of serum Te levels with aggression in children and adults [9,10] and the potential for a contribution of delayed/ advanced maturation in related conditions [11]. Thyroid function (thyroid stimulating hormone, TSH, free triiodo-thyronine, fT_3; and free thyroxine, fT_4) and growth factors (insulin-like growth factor I, IGF-I; insulin-like growth-factor binding protein 3, IGFBP-3), are associated with development and maturation. While thyroid resistance may [12] or may not be pertinent for CD or related disorders [13], short stature and delayed puberty may in some cases relate to unusual thyroid function [12] and to psychiatric features of personality development [14,15].

METHODS

Subjects

Subjects were 41 young male children and adolescents (10 to 17 years old). Diagnoses of consecutive referrals to the university clinic for child and adolescent psychiatry were made by two clinicians (ICD-10) based on a review of the patient history, behavioural observation during routine psychological testing, the short Conners parent-teacher rating scale (CPTQ [16]) and the child behaviour checklist (CBCL [17]).Externalising and internalising behaviour ratings were derived from the CPTQ and CBCL. The study group consisted of 28 CD patients free of medication: 19 had CD alone (F91.x), 6 had comorbid emotional (F92.8 and F92.9) and 3 had comorbid ADHD (F 90.1). The comparison group consisted of 13 healthy subjects (CON) without medical problems who reported to a general practitioner for a routine check and were age-matched with the patients. All subjects presented for a physical examination, ratings of sexual maturity and a blood sample (Table). Exclusion criteria were other major medical illness or psychiatric/ psychologic consultation. After obtaining approval from the clinic for the research, examination followed the consent of the child, the responsible adult and the therapist.

The Tanner scale for sexual maturation rates the degree of secondary hair growth, appearance of the scrotum and penis growth in 5 stages [18]. Maturity was classified as delayed or advanced if the ratings differed from the age-norm by *more* than one stage. For all controls ratings matched the norms for chronological age to within 12 months. No value exceeded 4 on this scale. Anthropometric measures included height, weight, chest circumference, leg-length, shoulder breadth and the inter-trochanteric distance. Height was measured with a Harpenden stadiometer, and other measures were obtained with calibrated clinical scales, and a tape measure. These measures were compared with the percentile ranges of a normal middle European population [19].

Blood Sample Analysis

Two blood samples were taken between 08.30 and 09.30 am. The first was collected in EDTA tubes and placed immediately on ice. Plasma was separated from blood cells within 3 hours and used to measure ACTH. Serum from the second

sample was used to measure the other hormones. Samples were stored at -20°C until analysis. The analysis used commercially available specific radioimmunoassay kits suitable for a paediatric endocrine laboratory without prior separation steps. The source, sensitivity and the intra-/ inter-assay variabilities (CV%) over the assay range were: ACTH (Nichols) 1 pg/ml, 5.4-5.8%, 3.2-4.9%; CS (Cortisol Bridge™, Serono) 1.9 ng/ml, 2.8-4.8%, 2.2-9.3%; DHEA-S (Sorin) 0.5 ng/ml, 4.3-4.8%, 8.9-9.4%; Te (Diagnostic Products) 6 ng/dl, 5.6-7.2%, 6.6-7.1%; E_2 (Sorin) 5.2 pg/ml, 5.8-7.1%, 7.2-8.9%; LH (MAIAclone™, Serono) 0.15 IU/l, 2.0-4.7%, 2.0-6.1%; FSH (MAIAclone™, Serono) 0.25 IU/l, 1.1-2.5%, 2.5-4.3%; PRL (MAIAclone™, Serono) 6.0 mIU/ml, 2.3-3.2%, 2.5-2.8%; TSH (IRMAclon™, Henning) 0.09 µU/ml, 1.2-6.2%, 2.4-9.2%; fT_3 (Brahms) 0.47 pg/ml, 2.8-4.2%, 3.2-6.3%; fT_4 (DYNOtest™, Henning) 0.1 ng/dl, 2.1-6.7%, 8.2-9.0%; IGF-I (IGFBP-blocked, Biomerieux) 0.02 ng/ml, 2.8-3.9%, 5.4-7.5%; IGFBP-3 (Biomerieux) 0.06 ng/ml, 4.8-9.68%, 9.5-14.1%.

Table 1. Data for healthy control (CON) and conduct-disordered (CD) subjects

Group		CON (N=13)			CD (N=28)		
		Mean	(SD)		Mean	(SD)	
Age (years)		13.9	1.5	10.7-16.8	13.2	(1.9)	10.0-17.8
Conners Scale	Restlessness	0.31	*0.48*		1.92	*0.85*	**
	Impulsivity	0.38	*0.51*		2.31	*0.84*	**
	Disturbs others	0.23	*0.44*		1.69	*1.0*	**
	Attention span	0.62	*0.65*		1.69	*1.0*	*
	Fidgetiness	0.08	*0.28*		1.38	*1.06*	**
	Distractibility	0.62	*1.0*		1.69	*0.93*	*
	Easily frustrated	0.46	*0.66*		1.92	*1.09*	**
	Easily cry	0.08	*0.28*		0.96	*0.82*	*
	Emotional lability	0.38	*0.51*		1.69	*0.93*	**
	Aggressive	0.31	*0.63*		1.85	*1.21*	**
	SUM	3.5	*3.3*		17.0	*5.5*	**
Stature (cm)	Height	168.1	*21.7*		161.0	*14.5*	
	Chest	85.4	*13.5*		81.6	*10.8*	
	Legs	90.9	*9.1*		85.2	*8.2*	#
	Shoulder	40.9	*6.5*		36.2	*3.8*	##
	Bitrochanter	34.0	*7.1*		28.4	*3.7*	##
Sexual Maturity	Normal (n, %)	7,	(54%)		21,	(75%)	
	Advanced	4,	(31%)		6,	(21%)	
	Delayed	2,	(15%)		1,	(4%)	

CON vs. CD,   * = $F(1,37) = 10.7$-14.0, $p < 0.002$,   ** = $[F(1,37) = 18.9$-$57.5]$, $p < 0.0001$;
$F(1,35) = 4.6$, $p < 0.04$; ## $F(1,35) = 7.5$-10.3, $p < 0.01$, with age as covariate.
[Student t-tests confirmed the probability levels to within 1%]

Data Treatment

Data from the Conners scale and the physical examination were examined by analysis of variance and the Student t-test. As data for only two subjects were in part missing and the variance of the data for 39 subjects was homogeneous, the effect of age was examined by a parametric analysis of covariance that confirmed the group differences. A mistake in sample-taking led to some missing hormone measures in up to 3 CD and 5 controls. Thus, this exploratory analysis of relatively small and uneven subject samples used non-parametric Mann Whitney U-tests. Spearman rank correlations are provided with a view to generating working hypotheses with trends cited as $p > 0.01$ and significant correlations as $p < 0.01$. As a check on developmental changes groups of CON and CD subjects younger and older than the control mean were also studied.

RESULTS

Behaviour, Stature and Maturity

Conners scores were higher for the CD than the CON group on each item (F [10,28] = 7.3, $p < 0.0001$; Table), especially for restlessness, impulsivity, fidgetiness, ease of frustration, disturbance of others and aggression. Externalising and internalising problems (CBCL) were evenly distributed: (scores were higher for internalising in 6, externalising in 9 and equivalent in 13 patients). Physical differences between the groups remained after covarying for age (F [5,31] = 6.0, $p < 0.0006$). The CD group had less broad shoulders, a smaller bitrochanter distance and shorter legs (Table). There were no differences in the degree of sexual maturation.

Hormone levels: Group comparisons

There were no group differences for gonadal steroids and gonadotropins (Fig.

1a). However, among the pituitary-adrenal hormones, DHEA-S showed a 50% increase (U = 109, z = -2.05, p = 0.04) and ACTH a 4-fold increase in the CD group (U = 17, z = -4.14, p < 0.0001). There were no differences for CS (Fig. 1a) or the thyroid hormones fT_4 and TSH, but fT_3 showed a 22% increase (U = 59, z = -2.69, p = 0.007) and the growth factors IGF-I and IGFBP-3 were elevated by 10% (not significant: Fig. 1b).

Hormone levels: relations to age

DHEA-S levels tended to increase with age in both groups (r = +0.33, p = 0.03, n = 41: Fig. 2). Higher levels were main-tained in younger and older CD children (< 14y, 6 CON/20 CD, 609 [SD 594] *vs.* 1187 [SD 662]; >14y, 6 CON/ 8 CD, 1200 [SD 604] *vs.* 1824 ng/ml [SD 640] (U = 32-11, z = -1.7, p = 0.09). In con-trast ACTH secretion did not correlate with age in either group, but like DHEA-S, higher levels were maintained in the younger and older patients (CD, 50 [SD 55] to 43 [SD 22] *vs.* CON, 6.5 [SD 6] to 12 [SD 17] pg/ml; U = 1-5, z = -3.2 to -2.2, p = 0.001-0.03). In controls, CS levels tended to correlate with age (r = +0.58, p = 0.05).

Levels of fT_3 were unrelated to age in either group. The higher levels in the CD group were restricted to the younger subjects (< 14y, 6 CON/17 CD, 3.3 [SD 0.8] *vs.* 4.5 [SD 0.7]; > 14y, 5 CON/ 8 CD, 4.0 [SD 0.9] *vs.* 4.4 [SD 0.5] pg/ml: U = 17, z = -2.6, p = 0.009). IGF-I levels (not IGFBP-3) increased with age in both groups (r = +0.45, p = 0.004, n = 41), and, like fT_3, levels tended to be higher in the younger patients (< 14y, 6 CON/ 20 CD, 153 [SD 122] *vs.* 256 [SD 130] ng/ml; U = 32, z = -1.7, p = 0.09). IGFBP-3 showed a similar trend in the young CD patients (3.3 [SD 1.0] *vs.* 4.1 [SD 1.1] mg/ml; MW U = 32.5, z = -1.7, p = 0.09).

PRL and E_2 levels increased with age more in the CD than the control group

(PRL; r = +0.45 [vs. +0.24], p = 0.003: E_2; r = +0.79 [vs. +0.21], p < 0.0001) attaining levels that tended to be higher in older CD vs. CON subjects (E_2, U = 9, z = -1.94, p = 0.05; PRL, U = 4, z = -2.58, p < 0.01).

Hormone levels: relations to physical and sexual maturity

There were no group differences in sexual maturity, but in the 6 CD and 4 CON children with accelerated maturity levels of LH, FSH, Te, E_2, IGF-1 were increased and CS decreased, as expected. The absence of correlations for these hormones with measures of physique in the CON group contrasted with clear relationships in the CD group that can only partially be accounted for by sample size. Thus LH, Te and E_2 correlated strong-ly with all five measures (r = +0.59 to 0.80, p = 0.001 to 0.00001). Less marked were correlations for each measure with DHEA-S (r = +0.35 [p = 0.06, legs] to +.56 [p = 0.002, chest] Fig. 2) and IGF-I (r = +0.38 to +.50, p < 0.036 to p < 0.1).

Hormone levels: relations to behaviour

Increasing sum scores of the Conners ratings (Table I) correlated with increasing levels of ACTH (r = +.48, p < 0.005, n=33, Fig. 2) and fT_3 (r = +.41, p = 0.01, n=36) with a trend relationship to DHEA-S levels (r = +.28, p = 0.08, n = 39). Correlations with symptom severity focused on DHEA-S, ACTH and fT_3. The following pattern

emerged with p < 0.01. ACTH was positively related to restless, impulsive and aggressive behaviour, fT_3 with fidgeting and DHEA-S levels were associated with disturbance-to-others (Fig. 2). Unique to the question, "does the child cry easily?" was a negative relationship to LH, Te and E_2 (r = -0.35 to -0.44, p = 0.008 to 0.03) with no relationship to other hormones.

Relationships between circulating hormone levels

Normal positive correlations were seen in both groups between hormones of the pituitary-gonadal axis (e.g., LH, FSH, Te, E_2, and PRL). These also correlated with the growth factors IGF-I and IGFBP-3 in both groups. Notable on the pituitary-adrenal axis was, a) the absence of a relationship between ACTH and CS, b) that DHEA-S correlated only with E_2 (both groups) and, in controls only, with IGF-I, and c) the growth factors and fT_3 (not TSH or fT_4) were inter-related in both groups. The CD group alone showed a relationship for fT3 with IGFBP-3 and a negative association for Te with TSH.

Fig. 1: On the left, levels of circulating corticotropin and steroid hormones; on the right, levels of growth factors and hormones of the thyroid axis in healthy control (CN) and conduct-disordered children (CD).
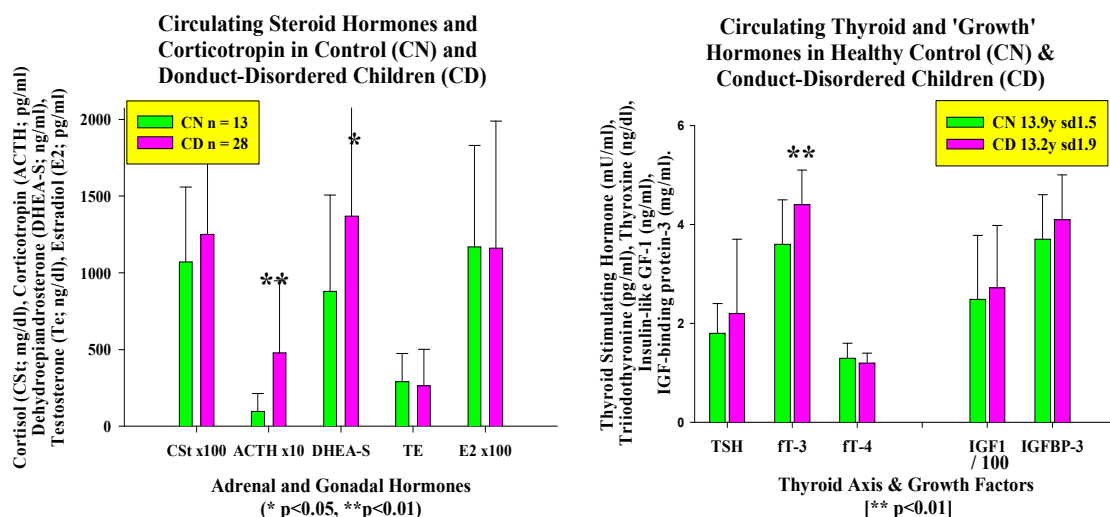

Circulating Steroid Hormones and Corticotropin in Control (CN) and Donduct-Disordered Children (CD)

CN n = 13
CD n = 28

Adrenal and Gonadal Hormones
(* p<0.05, **p<0.01)

Circulating Thyroid and 'Growth' Hormones in Healthy Control (CN) & Conduct-Disordered Children (CD)

CN 13.9y sd1.5
CD 13.2y sd1.9

Thyroid Axis & Growth Factors
[** p<0.01]

Fig. 2
On the left, Spearman correlations for DHEA-S with chronological age (top) and chest measurements (bottom) are compared for conduct-disordered (CD, symbol x: significant) and control children (CON, symbol •: non-significant). On the right Spearman correlations for DHEAS with the symptom "disturbs-others" (top), and ACTH with the sum of Conners symptom ratings (bottom)(+SD).
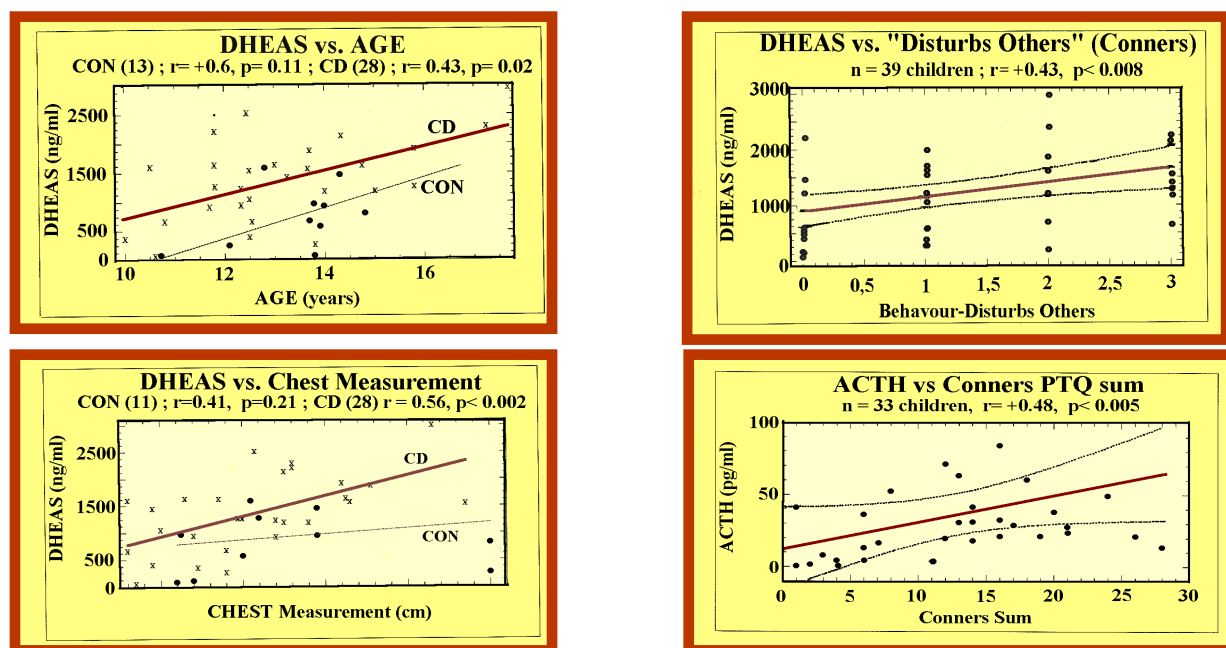
In summary, it is notable that where hormone levels differed between groups, there were unusual differences in the inter-hormone relationships. First, ACTH correlated with LH, FSH, PRL and Te only in the CD group. Second, the growth factors showed mixed relationships (with DHEA-S and PRL in controls only, or with fT_3 and IGF-I in the CD group only). Third, DHEA-S was associated with IGF-I in the controls but not in the CD group.

DISCUSSION

This sample of CD children was impulsive, restless and disturbed others: they tended to have smaller anthropometric measures but show similar levels of sexual development to normal age-matched children. The CD group showed increased levels of ACTH, DHEA-S, and the younger subjects small increases of fT_3, IGF-I and IGFBP-3. These hormone levels correlated with several indices of physical stature and psychopathology. But, gonadal hormone levels did not differ between groups and were not associated with signs of aggression. We discuss these findings in terms of the pituitary-adrenal, gonadal and growth hormone axes.

Increased ACTH levels were related to some ADHD-like features (restless, impulsive and some externalising behaviour): this parallels measures in adults with a potential for aggressive behaviour [20, 21]. The increased levels of PRL and ACTH in CD subjects could reflect low serotonin metabolism and thus reduced behavioural inhibition: negative correlations were reported for CSF serotonin metabolites of young persons with disruptive behaviour [22]. The absence of differences of CS levels is consistent with a study of ADHD children

with/without comorbid CD [8] and the absence of a correlation for increased CS with aggression in disruptive adolescents after a serotonin-releasing challenge with fenfluramine [23].

A change in ACTH levels without a rise for CS is not unusual. For example, voluntarily waking earlier than usual is preceded by increases of ACTH one hour before, without the CS changes that would accompany being awoken early [24]. ACTH levels rise in anticipation of having to cope with stress (e.g. wakefulness), CS levels reflect more a response to stress and activity. Here we find it telling that a) ACTH levels were associated with increased activity, b) associated PRL changes likely reflected decreased serotonin metabolism, associated with increased motor output [25] and reported from children with disruptive behaviour [22], c) increases of CS are enhanced by serotonin release that seems unlikely here [25].

Irritability and readiness to respond violently are reported from male adolescents [26] and adults [27] with high levels of Te. However, as with other studies of aggressive children [28, 29], we found that neither gonadal steroid levels nor the timing of sexual maturity was unusual in CD subjects. On the question of immaturity, it is interesting that CD children were rated highly for "crying", perhaps reflecting emotional immaturity and this feature correlated with decreased levels of LH, Te and E_2. Signs of delayed maturation and labile affect were described for teenagers with ADHD comorbid with personality disorders [30].

The unexpectedly high DHEA-S levels in pre- and postpubertal CD children contrast with a report of no differences in serum DHEA in prepubertal children hospitalised for aggressive behaviour [28], but parallel a report of nearly twofold increases in prepubertal 8-12 y-old CD

children [29]. Levels of DHEA-S and delta-5 androgens increase from about 6-8 years through puberty, reflecting maturation of the adrenal cortex, and then decrease in young adulthood. An increase, often independent of CS or PRL can be associated with hyperprolactinemia [31]. Thus, in view of a tendency for increased PRL levels in CD subjects, future studies should examine if changes of dopamine or serotonin activity, important in the control of PRL secretion, could underlie the endocrine changes.

What might an increase of DHEA-S in CD subjects reflect? Increases have been associated with self-confidence, an ebullient personality and extraverted aggression [32-34]. DHEA-S levels were also found to be high in male adolescents with schizophrenia [35]. Young male schizophrenic and CD patients share some early risk factors albeit for separate pathways of psychopathological development (e.g. dysfunctional families enhancing internalising and externalising features [3]). As laboratory studies of development have shown DHEA-S enhances neuronal survival and protects against neurotoxic insults [36,37] we predict that increased DHEA-S secretion may delay normal neurodevelopmental pruning processes.

Levels of IGF-1 and IGFBP-3, reliable indicators of growth hormone function, increase from 5 years through puberty and then decline across adult life. Increases of the IGF-I/IGFBP-3 ratio are seen in growth hormone deficiency [38] and may be associated with cognitive and mood changes in adults [39]. Our data confirm positive correlations in both groups for growth factors, age, sexual maturity ratings and LH secretion. Levels of both factors and IGF-ratios (CON, 67.3 vs. CD, 66.3) showed no signs of deficiency. Yet, there was a trend for

increased IGF-I levels in the younger CD subjects and for correlations with physique (like DHEA-S, Fig. 2). IGFBP-3 levels increased normally with age in controls, but in CD subjects levels were stable with age and correlated with fT_3 levels. Elsewhere differences in stature were not evident for patients with CD or related disorders [40].

Increases of fT_3 levels by a third in young CD is not inconsistent with a reported incidence of abnormal TSH, fT_3 or fT_4 levels in 35% of 193 adolescent psychiatric referrals [41]. The short stature and delayed maturity noted resembles very mild hypothyroidism. A degree of hyper- or hypothyroidism often accompanies other medical conditions and along with a euthyroid clinical status is not an indicator for intervention. Our data do not support a background of thyroid resistance in young persons with CD [12], even though associations for fT_3 with restlessness and impulsive behaviour are similar to data [12] for normal subjects.

In conclusion, these preliminary results show minor abnormal changes of adrenal-pituitary activity, indicative of a down-regulation and evident at the onset of adolescence in children with CD. Of these changes perhaps only the putative neurotrophic protective effect of high DHEA-S levels may have long-term consequences. These effects may include an alteration of the sensitivity of monoaminergic projection areas, where abnormal function has been related to conditions such as substance-abuse, a vulnerability for which CD is prognostic.

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