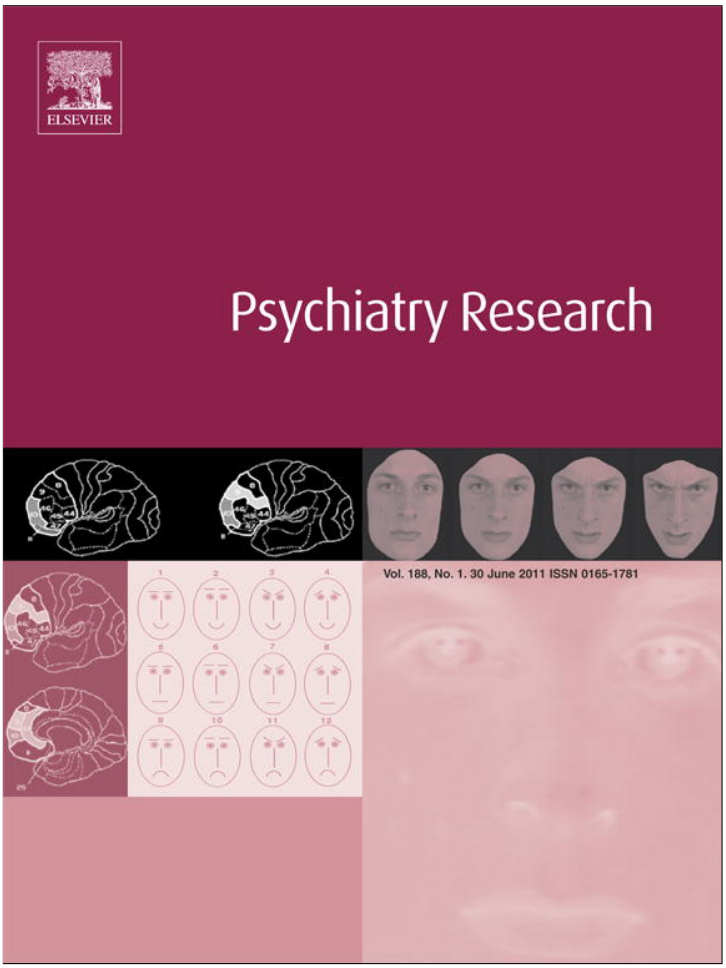

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Psychosocial dwarfism: Psychopathological aspects and putative neuroendocrine markers

Antonio Muñoz-Hoyos, Antonio Molina-Carballo *, MaríadelCarmen Augustin-Morales, Francisco Contreras-Chova, Ana Naranjo-Gómez, Fuensanta Justicia-Martínez, José Uberos

Unidad de Gestión Clínica de Pediatría, Hospital Universitario San Cecilio de Granada, Facultad de Medicina, Universidad de Granada, Spain

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ABSTRACT

There exists an extensive terminology for defining the situation of children who, in varying circumstances, suffer from affective deprivation (AD), within an unsatisfactory family situation or in institutions. Nevertheless, the neuroendocrine mechanisms (if they exist) determining it have yet to be identified. Our objective was to determine if specific neuroendocrine markers, all of them previously implicated in affective disorders, could be modified, and in which sense, in affective deprivation syndrome of the child. For this purpose, we studied three separate groups of children: (1) control group (CG); (2) children suffering from AD; and (3) children with non-organic failure to thrive (NOFT). In every case, we studied the serum levels of melatonin, serotonin, β-endorphins and adrenocorticotropic hormone (ACTH); and kynurenine pathway tryptophan metabolites (both during the day and at night). Significantly, there was a conspicuous reduction in the levels of each of the neuroendocrine markers (melatonin, serotonin, β-endorphins and ACTH) in the group suffering from affective deficiency, a diminution which was even more noticeable in the group of patients presenting delayed growth. Furthermore, as also occurs in other affective disorders, there were corresponding modifications in the metabolisation of tryptophan. We report the existence of neuroendocrine mechanisms that are associated with the above-mentioned clinical manifestations in these patients, mechanisms that may underlie the close connection existing between AD syndrome and the cause of NOFT. These data suggest that the AD syndrome and NOFT comprise a single process, but one with a different evolutionary continuum of psychosocial dwarfism.

1. Introduction

The psychosocial development of children is a complex process that may be negatively affected if it takes place in an environment where family relations are troubled or where affectivity is poor (Patton and Gardner, 1962; Masse, 1978; Mussen et al., 1979). At present, for diverse reasons, many children must be cared for within institutions that are specifically created and established to attend minors with family or social problems.

It is generally accepted that certain family situations (poverty, drug abuse, imprisonment, divorce, etc.) will probably have negative consequences on children's psychological and emotional balance (Bowlby, 1952; Casler, 1961; Rutter et al., 2007). The study of this pathology has led to the general acceptance of a syndrome that was previously described by a wide range of terms, including psychosocial dwarfism, litter digging syndrome, hospitalism, abandonism, reversible hyposomatothropism, non-organic growth retardation, non-organic delay in growth and development, affective deprivation (AD) syndrome, Kaspar Hauser syndrome, maternal deprivation, emotional deprivation, environmental growth failure, dwarfism due to deprivation and psychosomatic dwarfism due to abuse. This terminology is probably so heterogeneous due to a lack of unified criteria and to the wide range of professionals involved (psychologists, teachers, physicians, psychiatrists, endocrinologists, paediatricians, etc.).

From a pathogenic point of view, the situation is far from completely understood, although important contributions have been made (Wilcox et al., 1989; Blizzard and Bulatovic, 1992; Money, 1992; Voss et al., 1998; Muñoz-Hoyos et al., 2001). Early deprivation impairs regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, potentially increasing vulnerability to stressors throughout life. Basal cortisol levels in previously deprived children have shown contradictory results (Kertes et al., 2008; Fries et al., 2008; Bruce et al., 2009). Fries et al. (Fries et al., 2008) suggested that the nature and quality of the social and emotional caregiving received, not simply the duration of institutionalisation itself, may be a critical factor for predicting chronic hyperactivation of the HPA axis. In this sense, Bruce et al. (Bruce et al., 2009) found that foster children were significantly more likely than non-maltreated children to have low morning cortisol levels. In addition, foster children with low morning cortisol levels

* Corresponding athor. Departamento de Pediatría, Facultad de Medicina, Avda de Madrid 12, 18071-Granada, Spain. Tel.: +34 958023 660/996; fax: +34 958246661.
E-mail address: amolinac@ugr.es (A. Molina-Carballo).

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experienced more severe physical neglect than did the other foster children. By contrast, foster children with high morning cortisol levels experienced more severe emotional maltreatment (Bruce et al., 2009). Kertes et al. (Kertes et al., 2008) found no evidence that early neglect has long-term, direct impact on basal cortisol levels; but they noted that deficient care did significantly predict growth delay assessed at the time of adoption, while greater growth delay at adoption predicted higher early morning cortisol levels.

Among subjects who are susceptible to stress, a diet rich in carbohydrates increases the intracerebral concentration of tryptophan and of serotonin, and thus increases the serotoninergic neurotransmission that is capable of reducing both the hormonal response (cortisol) and the behavioural reaction to stress (Markus et al., 2000a,b), collaborating in the maintenance of homeostasis. On the contrary, stress (Muñoz-Hoyos et al., 2009) and/or a low level of tryptophan in the diet may commonly lead to a deficit of serotonin and melatonin; an insufficiency of these two hormones has been related to the onset of depressive disorders (Leyton et al., 1999). In healthy children, the nocturnal administration of tryptophan (Moreno-Madrid et al., 1999) or of pyridoxine (Muñoz-Hoyos et al., 1996) increases melatonin secretion. Melatonin, secreted nocturnally by the pineal gland among all animal species, has anticonvulsant (Molina-Carballo et al., 1994) and anti-stress properties that are partly attributed to its modulatory function within the central nervous system (Maestroni and Conti, 1991). It presents both hormonal properties, regulated through binding to a receptor, like any standard hormone, and also non-receptor-mediated properties (e.g., antioxidant properties), as it is capable of being readily disseminated to any organic compartment. Overall, melatonin acts as a synchroniser of biological rhythms, as an immunomodulator and as an antioxidant (Acuña-Castroviejo et al., 1995; Muñoz-Hoyos et al., 2007).

In the present work, we analyse if specific neuroendocrine markers, all of them previously implicated in mood disorders, could also be modified, and in which sense, in AD syndrome of the child. Further, we address the pathogenic similarities between the AD syndrome and non-organic failure to thrive (NOFT).

2. Methods

In the specialised health-care department at the San Cecilio University Hospital in Granada (Spain), which is part of the public health-care system of the region of Andalusia, and is responsible for a population of around 250 000, mainly of a low–middle socioeconomic level, we selected 72 children (whose demographic and anthropometric data are shown in Table 1), aged between 4 and 14 years, who were divided into two study groups.

2.1. Control Group

The control group (CG) consisted of 36 children (50% of the sample) all of the same age (± 6 months) and sex as each one of the patients belonging to the problem group. Selection criteria were: (1) no family antecedents of hereditary or neurological diseases; (2) normal birth; (3) no personal history of organic diseases, except childhood illnesses of favourable evolution always attended in primary care setting; and (4) normal neuromotor development and adequate educational performance.

2.2. Problem Group

The problem group comprised of the other 36 children. These patients were aged 4–14 years and constituted the entire population of the childcare institution; their average residence time was 34.7 months (range: 1 month–9 years) (Table 1), and over 16% of these children had been resident for over 5 years. We enrol only one child recently admitted to the institution (1 month). The other children had been institutionalised for more than 6 months. During the whole period of the study, all these subjects were cared for in the same boarding institution, for one or more of the following reasons: (1) parents addicted to drugs; (2) alcoholic parents; (3) single mother; (4) parents in prison; (5) Parent psychiatric illness; (6) lack of financial resources; (7) maternal mental deficiency; and (8) divorced or separated parents. Concordant to these data, the patients had a history of significant neglect, but not a known history of psychological or physical abuse, with no markedly disturbed and developmentally inappropriate social relatedness in most contexts.

None of these children had ever suffered serious diseases, or neurologic, endocrine or immunologic disorders, factors, which might bias the normal endocrine response. None of the patients had a known history of perinatal pathology, intrauterine growth retardation or physical signs suggestive of foetal alcohol syndrome.

For the sake of completeness and to distinguish between two very similar situations, although they present a different somatic expression (AD and NOFT), the problem group was divided into two subgroups: (1) the NOFT group, formed of 21 children presenting the fundamental characteristic of first-order somatometry (weight and height) lower than the third percentile for Spanish population, with no justifiable organic explanation, after application of the low stature protocol; and (2) a group of 15 children also living in an institution but presenting normal somatometry, although also with real evidence of affective deficiency (scored by State-Trait Anxiety Inventory for Children (STAIC) validated for the Spanish population by Seisdedos (1990) and Child Depression Scale, CDS (Tisher and Lang, 1978)).

2.3. Clinical method

Following the Helsinki criteria, with written informed consent obtained from the adolescent children and/or from tutors of the institution, we designed a working plan according to which the evaluation of each child was made at a different and suitable moment; all the parameters in this study (in all subjects) were determined from the remains of serum samples obtained for mild clinical reasons of prolonged course (fatigue, stomach ache, anaemic disorders, etc.) or as part of a routine whole health examination made by the primary care paediatrician responsible of the health needs of the institutionalised children. None of the samples was obtained in the setting of screening for acute or severe illness, nor did any of the subjects present acute high fever. During the day of the blood extraction (at 09:00), two separate samples of urine were taken: (1) day samples, comprising the urine excreted by the child between 09.00 and 21.00; and (2) night samples, consisting of the urine excreted between 21.00 and 09.00 the following day. This fractioned timing is essential from a methodological point of view, as it enables us to analyse possible circadian variations of the variances examined in this study. The analysis, nonetheless, consists of only two determinations, as for ethical reasons it is not possible to do otherwise during childhood.

2.4. Analytical Method

Melatonin, β-endorphins, serotonin and adrenocorticotropic hormone (ACTH) were determined by means of radioimmunoanalysis techniques (RIA), while kynurenine pathway tryptophan metabolites were determined by thin-layer chromatography, following the technique described by Coppini and Benassi (Coppini et al., 1959), as slightly modified by Núñez and Narbona (Narbona-López et al., 1986).

The measurement of melatonin was carried out by a commercial RIA kit (Euro-Diagnostics, Apeldoorn, the Netherlands). The cross-reactivity was less than 1% for related substances; with an inter-assay coefficient of variation (CV) of 9.5% at a concentration of 35 pg ml^{-1}. RIA for quantitative β-endorphin supplied by Inmuno Nuclear Corporation (Stillwater, MN, USA) has a lower limit of sensitivity of 8.6 pg ml^{-1}. The within-assay CV was less than 30%. Inter-assay CV was 3.3% at 18 pg ml^{-1}.

Table 1
Demographic and anthropometric data on the study groups.

	Control group	Problem group		*F*	*p*
	(*n* = 36)	AD (*n* = 15)	GR (*n* = 21)		
Age (y)	9.13 ± 3.6	8.73 ± 3.15	8.76 ± 2.9	0.61	0.54
Sex	19 F / 17 M	8 F / 7 M	12 F/ 10 M	-	-
Institutionalization duration (m)	-	19.82 ± 9,53	45.33 ± 18.54	23.77	<0.001
Height (m)	1.33 ± 0.14 (<50)	1.28 ± 0.17 (<25)	1.2 ± 0.14 (<3)	24.1	<0.001
Weight (kg)	30.95 ± 11.4 (>25)	26.46 ± 8.65 (<25)	19.9 ± 5.92 (<25)	8.88	<0.001
BMI (kg/m^2)	17.2 ± 2.6 (<50)	15.35 ± 1.8 (>10)	13.43 ± 1.72 (<3)	20.47	<0.001
GH (ng/ml)	3.9 ± 1.17	4.02 ± 2.89	3.49 ± 1.66	2.06	0.13
WISC-IV (>5 y)	103 ± 9.5 (>50)	89.9 ± 10.3 (>25)	80.6 ± 16.4 (>10)	23.91	<0.001

Data shown as mean ± standard deviation. Percentile ranks (based in published data for Spanish population) of the mean are shown between parentheses. F: female; M: male. GH: basal growth hormone, that show no differences between groups. WISC-IV: Revised Wechsler Intelligence scale, total score.

Serotonin RIA kit purchased from Labor Diagnostika Nord GmbH & Co. KG has an intra-assay CV of 4.7 and an inter-assay CV of 5.6. ACTH was measured by immunoradiometric assay (ELSA-ACTH, CIS-Biointernational, Gif-sur-Yvette, Cedex, France) with an intra-assay CV of 3.7 and inter-assay CV of 3.8. Serum growth hormone (GH) was measured previously to the inclusion in this study, by RIA (Sorin Biomedica, Saluggia, Italy) with an intra-assay CV of 2.3% and inter-assay CV of 5.4%.

2.5. Statistical Method

The data obtained are expressed in the units corresponding to each variance as the mean ± S.D. Statistical analyses included the Student's *t*-test and analysis of variability by one-way analysis of variance (ANOVA) with *post hoc* comparisons (Bonferroni test, T3 Dunnet), for normal variables (as defined by the Shapiro–Wilk test). For variables that did no meet the ANOVA assumptions, we used non-parametric methods such as the Kruskal–Wallis one-way ANOVA, with *Z*-values of Kolmogorov–Smirnoff test for pair-wise samples comparisons. We performed all tests with Statistical Package for Social Sciences (SPSS) statistical software, version 15.0.

3. Results

The demographic and anthropometric data of the study groups are summarised in Table 1. The results of the neuroendocrine variables selected on the study groups are expressed as the mean value for each group ± S.D., in the units corresponding to each of the variables studied for the serum or plasma samples (Table 2). Analysis of these data revealed the following:

ACTH: The production of ACTH was notably higher in CG ($F = 20.6$; $P<0.001$). The Bonferroni test showed that these differences exist between CG and NOFT ($P<0.001$) and between CG and AD ($P<0.001$).

β-Endorphins: We obtained a value of $\chi^2 = 35.92$ ($P<0.001$), with differences between CG and NOFT (Z: 2.89; $P<0.001$) and between AD and NOFT (Z: 2.22; $P<0.001$), with no differences between CG and AD (Z: 0.759; $P = 0.612$).

Melatonin: This methoxyindol presented a very similar reaction to that of the above-described variances, with an F value of 27.86 ($P<0.001$). Even though this was obtained during the day, it is still of great interest. The *post hoc* analysis by T3 Dunnet showed that differences existed between CG and the other two study groups, with a value of $P<0.001$ in each case. The results for ACTH, β-endorphins and melatonin are summarised in Fig. 1.

Serotonin: Similarly, in samples drawn during the morning, the production of 5-hydroxy-tryptamine was significantly higher among the CG ($\chi^2 = 56.09$; $P<0.001$), with differences between CG and NOFT ($Z = 3.62$; $P<0.001$), between CG and AD (Z: 2.87; $P<0.001$) and between NOFT and AD (Z: 2.62; $P<0.001$); Table and Fig. 2.

Table 3 shows the data corresponding to the kynurenine pathway tryptophan metabolites determined in urine samples obtained during the day and night. These data are expressed as the mean of each group and its S.D., together with the level of statistical significance. No significant differences between the groups were observed in any of the metabolites examined during the day. At night, significant differences were found between groups for kynurenic acid ($\chi^2 = 59.28$; $P<0.001$), xanthurenic acid ($\chi^2 = 50.86$; $P<0.001$) and anthranilic acid ($\chi^2 = 42.11$; $P<0.001$).

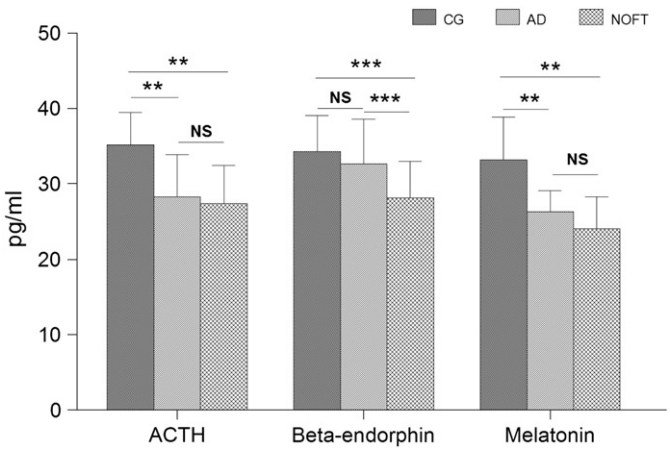

Fig. 1. Neuroendocrine data that allows us to differentiate between children with affective deprivation and those with non-organic failure to thrive. There is also an intermediate situation related to each one of the mediators studied in children who only present affective deprivation (*** = P<0.001, ** = P<0.01, NS= non-significant). These serum samples were taken at 09:00 h. CG: control group, AD: affective deprivation group, NOFT: non-organic failure to thrive group.

4. Discussion

Our data show a significant reduction in the levels of each of the neuroendocrine markers previously studied as possible markers of mood disorders, in children with affective deficiency (AD). Melatonin, serotonin, β-endorphins and ACTH in the group of children suffering from AD, a situation of chronic stress, a diminution which was even more noticeable in the group of patients presenting delayed growth. The organic incapability of confronting stress on a genetic basis, and/or the fact of repeated stresses, from exhaustion of the homeostatic mechanisms, could make some groups of patients liable to suffer depressive symptoms associated with a wide range of deleterious consequences in the neurological field (delayed learning), in the endocrine system (delayed growth) or in the immune system (repeat infections). All these diseases are present in AD. This latter assertion is supported by the related literature, as well as by certain experiments carried out in our group, and by the data provided here. In this sense, Sonuga-Barke et al. (Sonuga-Barke et al., 2008) assessed that duration of deprivation was associated with smaller head circumference, lowered intelligence quotient (IQ) and increased mental heath problems, independently of effects found for subnutrition on head circumference and IQ.

We have observed a diminution of such important markers as 5-hydroxy-tryptamine, β-endorphins, melatonin and ACTH; in children with AD, which is more evident in the case of NOFT. Other neuroendocrine markers, which may also be involved include leptin and brain-derived neurotrophic factor (BDNF) that interplay with serotoninergic neurotransmission (Shaoul et al., 2003; Ehrlich et al., 2009). For the above reasons, we believe this is a single disease or situation but one presenting two different stages of evolution, and

Table 2
Plasma / serum metabolites en samples taken in the morning (mean ± SD; pg/ml) in each of the groups studied.

	CG ($n = 36$)	Problem Group		Statistical test*	*p*
		AD ($n = 15$)	NOFT ($n = 21$)		
ACTH	35.14 ± 4.29***	28.24 ± 5.67	27.36 ± 5.03	$F = 20.6$	<0.001
Beta-endorphin	34.24 ± 4.81	32.6 ± 5.97	28.14 ± 4.81†	$\chi^2 = 35.92$	<0.001
Melatonin	33.19 ± 5.62***	26.24 ± 2.83	24.04 ± 4.2	$F = 27.86$	<0.001
Serotonin	229 ± 56.54***	124.66 ± 19.31	74.76 ± 18.31	$\chi^2 = 56.09$	<0.001

*Cross-sectional analyses were conducted by analysis of variance (ANOVA-I) with post-hoc comparisons based in Bonferroni's method for ACTH and in Dunnett-T3 test for melatonin. For the beta-endorphin and serotonin analysis we used Kruskal–Wallis 1-way analysis of variance, with Kolmogorov–Smirnov test for pair-wise comparisons. *** = P<0.001 vs AD and GR groups; † = P<0.01 vs CG and AD groups.

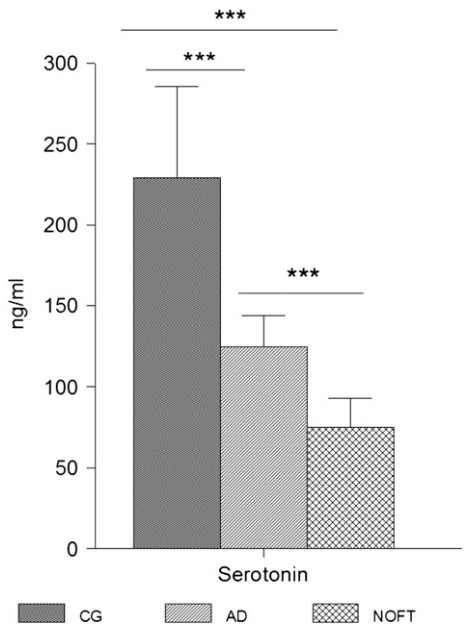

Fig. 2. Serum determinations of serotonin (09:00 h) in normal children (left), those with affective deprivation syndrome (centre) and those affected by non-organic failure to thrive (left), (***$P<0.001$). These serum samples were taken at 09:00 h. CG: control group, AD: affective deprivation group, NOFT: non-organic failure to thrive group.

consequently, one that expresses different clinical possibilities. This assertion means that there must exist a pathogenic substratum to explain such an evolution. We do not accept the classical hypothesis, which maintains that exclusively nutritional or digestive disorders are responsible, as nutritional supply and state can vary substantially. We believe it is possible to outline a 'psycho-neuroendocrine' hypothesis based on the following arguments: (1) the permanent situation of strain and worry most of these children live in can be considered as an authentic pattern of chronic stress; indeed, we have observed that particular markers of the response to stress (Fig. 1) present an evidently lower level of peripheral response than that of a reference child population; (2) some findings for children with AD and NOFT in relation to circulating levels of melatonin (Fig. 1) and serotonin (Fig. 2) are closely related to the indoleaminic theory of mood disorders, in such a way that the possibility of a connection between mood disorders in children and the metabolism of certain indoleamines must be admitted; Further, in adult patients, reports have been made of a relation between some types of depression and reduced levels of melatonin (Weterberg, 1985), and that an initial reaction to stress combined with the development of resistance to corticotropin-releasing hormone (CRH) may be related to a low-melatonin syndrome in some patients suffering from depression (Wahlund, 1999); and (3) the results shown in Table 3 demonstrate the validity of the circadian variation in tryptophan metabolisation routes – though of a lesser intensity in these cases – and of the theory of the 'double lock gate' in relation to the different metabolic ducts of tryptophan (Muñoz-Hoyos et al., 1998, 2009). In this sense, we should remember that, for some time, treatment modes for depressive patients have involved the use of tryptophan as a substratum of the metabolic tracts presented in this study. With respect to the ACTH and serotonin modifications, some experimental studies in this field have achieved results compatible with the neuroendocrine modifications presented here (van Oers et al., 1998; Vazquez et al., 2000).

Returning to the subject of symptomatic plurality, Skuse et al. (Skuse et al., 1996) studied a group of children with NOFT associated with conditions of psychosocial stress. Contrary to other descriptions, concomitant symptoms with delayed growth were hyperphagia and polydipsia, in singular contrast to the anorexia found in other cases of delayed growth of identical aetiology (Tarren-Sweeney, 2006). Skuse et al. (Skuse et al., 1996) noted that when children were separated from stressful family circumstances, the insufficiency of GH was resolved spontaneously in a considerable number of cases. Three decades earlier, Silver and Finkelstein (Silver and Finkelstein, 1967) remarked that these manifestations should be considered as one of the aspects of the psychosocial syndrome, and that all the symptoms, including behavioural ones, are related to the primary cause: the inadequate family psycho-affective background, which is an illustrative proof of the symptomatic plurality inherent to the process.

In his study of four cases of psychosocial dwarfism, de Kerdanet et al. (de Kerdanet et al., 1993) did not find the classical pattern of rapid behavioural improvement and normalisation of serum levels of GH, when the causes of stress alter or disappear. These authors did not conclude this to be a clinical–idiopathic or essential state, but considered rather that, in certain children, the original psychosocial disturbance might lead to severe psychopathological troubles, requiring therapeutic treatment in specialised institutions. In the prognosis factors described by our group (Muñoz-Hoyos et al., 2001), we pointed out that the duration of the adverse situation is closely related to the reversibility of its negative effects; thus, in cases of long duration, subsequent recovery may only be partial.

Other significant considerations include: (1) the substantial changes undergone in children's institutions, both in their conception and in the infrastructure of staff and facilities, modifications such that on many occasions the institutionalisation 'in itself' does not play a negative role in different aspects of infantile growth and development (Powell, 1988; Contreras Alemán, 1997); (2) the dynamic and changing nature of the process by which family, social, affective, institutional and personal factors interrelate to create a situation that may offer different clinical manifestations (Powell, 1988; Molina-Font and Muñoz-Hoyos, 1998; Gilmour and Skuse, 1999); (3) When Bowlby indicated "there is a specific relation between deprivation during the first years in life and the development of psychopathic and anti-affective character tending to delinquency difficult to treat," these views were probably overplayed and, consequently, the role of

Table 3
Urinary excretion of kynurenine-pathway tryptophan metabolites (mean ± SD; μg/ml) in each of the groups studied, in urine samples obtained during the day (09.00-21.00) or night (21:00-09:00) hours.

	CG ($n=36$)		Problem Group				χ^2	p
			AD ($n=15$)		GR ($n=21$)			
	Day	Night	Day	Night	Day	Night		
Kynurenine	4.68 ± 1.8	3.06 ± 0.61	4.8 ± 1.85	3.9 ± 2.13	5.51 ± 2.17	5.03 ± 2.92	3.80	0.149
Hydroxykynurenine	14.03 ± 5.01	9.63 ± 2.05	13.63 ± 5.35	12.14 ± 6.64	17.37 ± 6.89	14.86 ± 8.84	1.46	0.482
Kynurenic acid	14.88 ± 5.35	11.76 ± 2.51***	14.76 ± 5.41	38.72 ± 22.62†	17.95 ± 6.56	112.71 ± 19.66‡	59.28	<0.001
Xanthurenic acid	15.44 ± 5.52	9.75 ± 2.29***	15.41 ± 5.33	137.5 ± 77.82†	17.44 ± 6.66	149.47 ± 54.34§‡	50.86	<0.001
Anthranilic acid	1.8 ± 0.87	1.2 ± 0.37***	1.76 ± 0.5	5.58 ± 1.96†	2.12 ± 0.95	2.18 ± 1.14‡	42.11	<0.001

*Cross-sectional analyses were conducted by Kruskal–Wallis 1-way analysis of variance, with Z values of Kolmogorov-Smirnov test for pair-wise comparisons. *** $P<0.001$ vs night AD; †$P<0.001$ vs night GR; ‡$P<0.001$ vs night CG; §$P<0.01$ vs night AD.

other factors was undervalued, thus giving rise to the current terminological confusion (Bowlby, 1973).

In the light of these considerations, and of our own revision of the subject, we believe that, in paediatric terms, the problem should be addressed under the following conceptual approach: (1) the existence of certain predisposing factors (social, family, affective and institutional) will be experienced in a different way by every child, and the entirety of this environmental and individual interaction, and of the greater or shorter duration of internal mechanisms (which are not yet well understood) will facilitate a wide range of clinical possibilities, such as effects on growth, development, psycho-affective state, personality and sociability, among other manifestations; and (2) the dynamism of the process and the prolongation in time, fundamentally, is the key to a more or less accentuated AD and will lead to the development of biological mechanisms, finally producing organic repercussions that, in extreme circumstances, will give rise to true dwarfism in the child (weight and height below the third percentile), with no demonstrable organic cause (NOFT).

The current information available does not enable us to make a clear distinction between AD and NOFT. Although these terms seem to refer to two unrelated diseases, the literature often makes allusions by which it is understood that these two terms are used in reference to the same situation. In this sense, Wilcox (Wilcox et al., 1989) reviewed the literature and concluded that concerning this important childhood problem there exists a "lack of unity of criteria," which has led to the non-existence of a scientifically acceptable exact definition. The data presented here support our view of AD and NOFT as a single process, but one with different evolutionary stages of psychosocial dwarfism. This clinical entity appears to be separate from reactive attachment disorder (RAD) based on the known data of the clinical history and clinical characteristic of the patients.

We have established: (1) the important role played by the long-term duration of both mood disorders and of other predisposing negative factors in the evolution of the continuum process from 'affective deprivation syndrome' towards 'non-organic failure to thrive syndrome'; (2) when NOFT exists, we have found that, as described in the literature, this situation can be considered reversible; thus, if the negative environmental and affective conditions disappear, recovery of growth indices may be expected; and (3) at the level of the neuroendocrine and metabolic response, there exists a range of differences between the normal child, the child suffering from AD and the child with NOFT.

4.1. Limitations

We know as limitations of our study that: (1) the mood disorders in children have a multifactorial aetiology; thus different aetiologies can influence the development from the moment of conception (e.g., maternal nutritional factors, which can induce long-lasting epigenetic modifications (Chmurzynska, 2010)); and, therefore, we cannot determine the aetiology nor quantify the contribution of neuroendocrine changes described in this work; (2) although this is a cross-sectional study conducted in a short interval time, the '*n*' of the sample is relatively small; and (3) the reliability of the information about the personal background of the patients in problem groups (data prior to the institutionalisation) is weak, given the lack of a written clinical report, precluding the possibility of establishing an alternative diagnosis according to the criteria defined by Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Our patients did not meet the DSM-IV-Text Revision (DSM-IV-TR) and International Classification of Diseases (ICD)-10 criteria for RAD, a clinical entity of infancy or childhood with onset before 5 years of age, defined as a commission disorder rather than an omission disorder, although abuse by itself does not lead to attachment disorder.

4.2. Conclusion

We are convinced that we are facing a unitary syndromic reality, the proper definition of which requires further research into the causal factors and into the pathogenic mechanisms that may bring about clinical consequences. From this knowledge, we must then seek therapeutic solutions to minimise the adverse effects suffered by children.

Conflict of interest

None.

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