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ORIGINAL ARTICLE

Evidence of pineal endocrine hypofunction in autistic children

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Abstract

OBJECTIVE: The pineal hormone melatonin (MLT) has been proven to play a fundamental physiological regulatory role on both biological and psychic functions and alterations of the light/dark circadian rhythm of MLT have been described in several chronic immunoinflammatory diseases and in psychic disorders. Aim of the present biological explanatory study was the evaluation of MLT circadian rhythm in autistic children, in order to preliminary assess the pineal endocrine function in the autistic syndrome.

METHODS: The study included 14 children suffering from classical infantile autism, who were investigated for the whole 24-hour circadian rhythm by collecting venous blood samples at 4-hour intervals. Serum levels of MLT were measured by the RIA method. The control group consisted of 20 age-matched healthy children.

RESULTS: No autistic patient showed a normal MLT circadian rhythm. Moreover, autistic children showed significantly lower mean concentrations of MLT, mainly during the dark phase of the day, with respect to the values observed in the controls.

CONCLUSION: The results of this preliminary study suggest the existence of a pineal endocrine hypofunction in autistic children, whose pathophysiological significance needs to be thoroughly investigated in successive clinical studies.

Introduction

The recent advances in Psychoneuroendocrinology have allowed us the possibility to analyse the neurobiochemical basis of emotions and consciousness status. In particular, several experimental and clinical studies have emphasized the importance of the pineal gland in the neurobiochemical regulation of consciousness processes and of other fundamental biological functions [1]. The circadian release of melatonin (MLT), the most investigated pineal hormone [2], with high levels during the night and low concentrations during the light phase of the day, has appeared to be fundamental in the regulation of biological rhythms and of interactions between psychic condition and environmental factors [3]. The light/dark circadian rhythm would represent the main factor regulating the pineal endocrine activity [2]. However, several other exogenous and endogenous factors have been proven to influence the pineal gland and MLT release, including magnetic fields, immune status, hormones and neuropeptides [1]. Therefore, the release of MLT would constitute the algebric synthesis of several inhibitory or promoting stimulations. Moreover, the amounts of MLT released from the pineal gland may change during one's lifetime. In particular, MLT production progressively decreases with age [4], mainly during the night, whereas it is highest in the prepubertal period of one's lifetime [5, 6]. In more detail, the decline in the nocturnal peak of MLT would constitute one of the first clinical signs of the pubertal onset [6].

According to the actual status of knowledge, the evidence of a physiological light/dark rhythm of MLT seems to represent an essential biomarker of the status of health, either in animals or in humans [1]. Even though there are individual variations, it has been shown that MLT circulating concentrations during the night have to be generally at least three times greater than those detected in the blood during the light phase of the day [2]. The statement that the evidence of MLT circadian rhythm is a fundamental marker of the status of health is justified by the fact that several biological or psychic diseases may be characterized by an altered MLT light/dark rhythm, including advanced cancer [7], ischemic cardiac disturbances [8], depression [9] and headaches [10]. The lack of nocturnal increase in MLT blood concentrations would constitute the most common pineal endocrine alteration described up to now in humans [1].

As far as the autistic syndrome is concerned, at present there are no clear data about the pineal function in children with classical infantile autism. However, because of the importance of the pineal gland in the regulation of the psychobiological unit, the profound alterations, which characterize the autistic syndrome and which may involve both status of consciousness and biological rhythms, namely the sleep/awake rhythm, could at least in part be due to a possible pineal damage and in any case justify the investigation of the pineal endocrine activity in this severe and dramatic human disease. This statement is further justified by the recent evidence of the autism-related immune dysfunction [11, 12], on the basis of the well demonstrated fundamental role of the pineal gland in the psychoneuroimmune activation of the immune system [13]. The present preliminary study was performed in an attempt to evaluate the pineal endocrine function in a group of patients with classical infantile autism (CIA), by analyzing the light/dark rhythm of MLT, which represents the most commonly used clinical test available up to now to explore the pineal endocrine status [2].

Materials and Methods

The study included 14 consecutive untreated autistic children (M/F: 11/3; median age 7 years, range 5-10), who were admitted at the Infant Neuropsychiatric Division of Monza Hospital for their disease. All patients were prepubertal subjects. The diagnosis of CIA was established according to DMS-IIIR criteria, after the evidence that all hematological and radiological examinations, including brain CT scan, were within normal range.

To evaluate MLT circadian rhythm, peripheral venous blood samples were collected through an indwelling cathether at 8 AM, 12 PM, 4 PM, 8 PM, 12 AM and 4 AM. No patient was under therapy with drugs which influenced the neuroendocrine system during the study. The control group consisted of 20 age- and sexually stage-matched healthy children. Both subjects and patients led a normal life rhythm and were exposed to light for a period of 14 hours and to complete darkness for the remaining 10 hours. Serum levels of MLT were measured by the double antibody-RIA method and commercially available kits. All samples were measured in duplicate. Intraassay and interassay coefficients of variation were 4% and 5%, respectively. The sensitivity of the assay was 1 pg/ml. Data were reported as mean $\pm$ SE and statistically analyzed by the Student's T-test and the analysis of variance, as appropriate.

Results

All healthy controls showed a physiological increase in MLT concentrations during the dark period of the

day, with values at least 3 times greater with respect to the levels observed during the period of maximum light. In contrast, none of the patients showed physiological increase in MLT concentrations during the night. In more detail, 10/14 patients showed no daily variations in MLT blood levels, whereas the remaining 4 patients had higher levels of MLT during the period of maximum light rather than during the night, as in healthy subjects. In addition, patients with inverted circadian rhythm of MLT showed more pronounced sleep disturbances than those with no daily variation in MLT levels. Mean values of MLT observed during the 24-hour rhythm in patients and controls are illustrated in Fig. 1. The mean concentrations of MLT observed in autistic patients were significantly lower than those found in healthy controls during the whole 24-hour circadian rhythm, with the greatest statistically significant difference during the dark period of the day ($P < 0.001$ vs. controls).

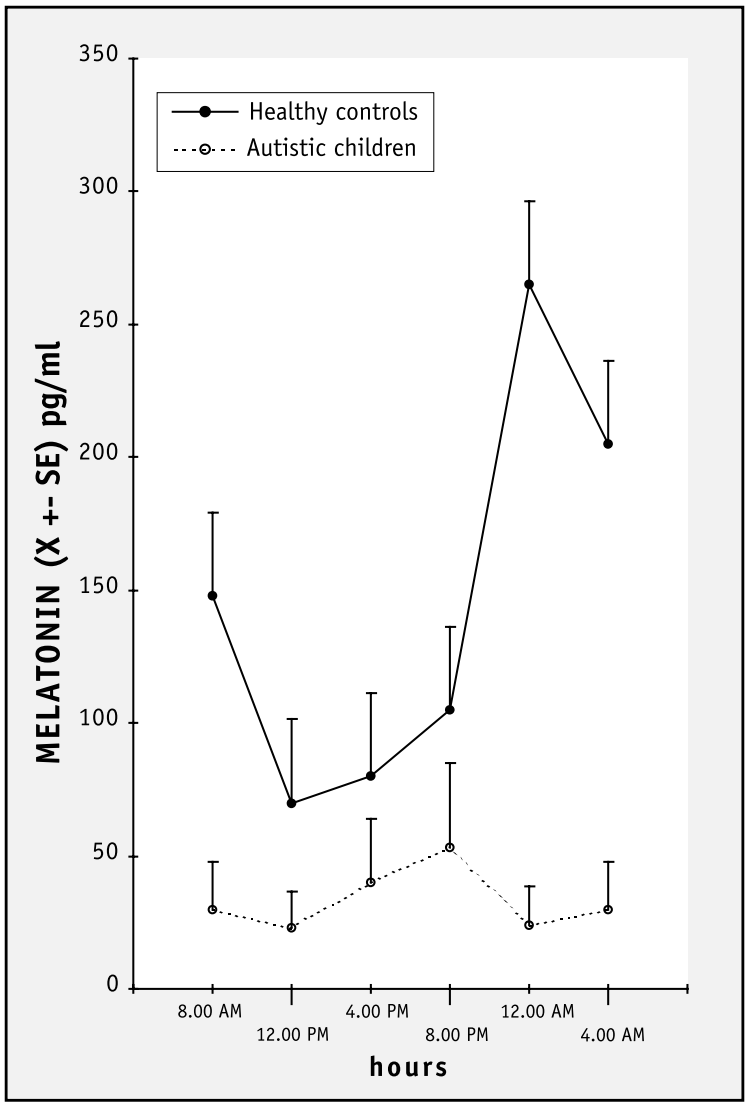

Fig. 1. Mean serum concentrations of melatonin observed during the 24-hour circadian rhythm in healthy subjects and autistic children.

Moreover, after the study, the exogenous administration of MLT (5 mg/day orally in the evening) seemed to improve sleep disturbances in 2 out of 3 patients with more pronounced disorders.

Discussion

The results of this preliminary study suggest that the infantile autism seems characterized by an evident damage of the pineal endocrine activity, consisting of both qualitative and quantitative disorders of MLT secretion. In other words, both altered light/dark rhythm and deficiency of MLT secretion may characterize the autistic syndrome. Obviously, the clinical significance of the pineal hypofunction in the pathogenesis and pathophysiology of the autism needs to be understood by future studies. However, because of the pineal known role in the regulation of sleep rhythm [1], MLT deficiency should be at least considered as a possible mechanism of autism-related sleep disturbances. In addition, other findings suggest an involvement of pineal disturbances in autistic syndrome: for example, several immune alterations may be observed in autistic children, mainly consisting of an unbalanced T helper-1 (TH1) to T helper-2 (TH2) lymphocyte ratio [12], with TH2 hyperfunction and TH1 hypofunction, and a consequent diminished production of IL-2. Since it is known that the immunomodulatory effects of MLT mainly consist of stimulation of TH1 functions and IL-2 secretion [13], MLT deficiency could play a part in the autism-related TH1 hypofunction.

Successive explicative studies on a larger number of patients are required to better understand and define the pathophysiological significance of MLT deficiency occurring in the autistic syndrome, as well as to establish whether the evidence of a pineal hypofunction may simply represent an epiphenomenon related to other major neurobiochemical anomalies, or whether it may play a role in the pathogenesis of autism. In fact, MLT is not the only pineal hormone provided by both biological and psychomimetic effects, and at least two other pineal indoles have to be considered, 5-methoxytryptamine and 5-methoxytryptophol [14], characterized by antidepressant activity and capacity of enhancing the mind concentration, respectively. Therefore,

further studies concomitantly evaluating the whole pineal function, through the assessment of circadian secretion of MLT, 5-methoxytryptamine and 5-methoxytryptophol, are worth better defining the degree of pineal damage occurring in the autistic syndrome, as suggested by our preliminary results, and to point out further possible pineal indole alterations in addition to that of MLT itself. According to our preliminary results, the evidence of no nocturnal MLT increase in the autism would suggest that the autistic children may be unable to differentiate the light from the darkness from a psychoneuroendocrine point of view, and this alteration would biochemically reflect the alterations involving the status of consciousness, which characterize the autistic syndrome.

Finally, if these findings will be confirmed in a larger number of patients, further studies in clinical settings with endocrine replacement therapy by exogenous MLT given during the dark period of the day are worth verifying whether the replacement of physiological light/dark circadian rhythm of pineal function may induce clinical benefit in autistic syndrome.

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