Increased slow wave sleep in a hypopituitary dwarf

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Summary

The main features of the nocturnal EEG of a dwarf with evidence of hypothalamic disease were an increase in slow wave sleep (SWS), a reduction in stage 2 and no alteration in total rapid eye movement. Administration of growth hormone caused a further increase in SWS time.

Introduction

A high incidence of EEG abnormalities have been reported in pituitary growth disturbances (Stoian *et al.*, 1969); these are associated with retardation of cerebral maturation and are poorly responsive to growth hormone (GH) treatment (Surwillo, 1978). Sleep EEG studies have not been reported in these patients.

Case report

In 1970, a 10-year-old male presented with dwarfism. Hypothyroidism was noted and insulin hypoglycaemia failed to stimulate GH release. L-Thyroxine 0.05 mg daily was commenced. No increase in height velocity followed.

Five years later he was referred to the Endocrine Pharmacology Unit, St James's Hospital, Dublin, and was 119.5 cm in height (4.1 s.d. below the 3rd centile), he weighed 22.35 kg (50% less than the 3rd centile) (Tanner, Whitehouse and Takaishi, 1966). In the previous 5 years he had grown 2.8 cm/year. Bone age was 10.5 years and X-rays of the pituitary fossa were normal. Full scale i.q. was 75. Physical examination was otherwise normal.

GH deficiency was suggested by a peak response of 1.1 mu./l GH to a glucagon 1 mg i.m. stimulation test lasting 3 hr. Following the administration of 6 mg human GH daily, mean urinary nitrogen excretion fell from a control mean of 6.2 g daily to 2.45 g daily, demonstrating a positive end-organ response. Hyperprolactinaemia was shown by a serum prolactin of 57 ng/l (normal range < 8 ng/l). The serum cortisol at 9 a.m. varied between 170 and 230 nmol/l (normal range 193-607 nmol/l) on

different mornings while ACTH levels were within normal limits. Hypothyroidism was suggested by a serum thyroxine of 55 nmol/l (normal range 60-140 nmol/l). The thyroid stimulating hormone (TSH) level rose from 2.5 mu./l to 36.9 mu./l at 20 min and 45.8 mu./l at 1 hr following stimulation by thyrotrophin-releasing hormone (TRH) (200 i.u. i.v.). This delayed response suggested a hypothalamic lesion (Hall *et al.*, 1972). During a luteinizing hormone releasing hormone (LHRH) test (100 µg i.v.) the follicle stimulating hormone (FSH) level rose from 1.0 mi.u./ml to a peak of 2.4 mi.u./ml at 60 min and the LH level rose from 0.04 mi.u./ml to a peak of 4.5 mi.u./ml at 30 min. This was a normal prepubertal response to LHRH (Savage *et al.*, 1978). Plasma electrolytes and urinary osmolality after overnight water deprivation were normal.

Sleep electrophysiological data were recorded on 4 nights from midnight to 8 a.m. and scored according to the Rechtschaffen and Kales (1968) criteria, with slow wave sleep (SWS) encompassing stages 3 and 4. The first 2 nights were control nights. On night 3, 30-min blood samples were taken for GH analysis without disturbing the patient, from an indwelling catheter placed in a cubital vein. No nocturnal rise in GH occurred despite the abnormally high SWS time. On night 4 GH (6 mg i.m.) was administered at midnight to determine whether there was any feedback effect on the sleep pattern. The results of the sleep data are shown on Table 1. The laboratory range of sleep stage values for age and sex matched normal controls is also shown.

Treatment with GH (8 mg) thrice weekly was commenced and L-thyroxine (0.1 mg/day) continued. Longitudinal growth rate increased to 8.4 cm/year during the following 3 years. Bone age increased to 14 years and on physical examination, stage 2 pubertal changes were evident. The full scale i.q. had increased to 85. During this time the morning plasma cortisol continued at a low normal level.

Discussion

Growth retardation due to hypopituitarism is most commonly due to an underlying hypothalamic

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TABLE 1. Sleep data as a percentage of the total night's sleep before and after growth hormone

	Normal subjects Mean ($\pm$ s.d.)	Patient			
		Night 1	Night 2	Night 3	*Night 4
Sleep stage 1	7.5 (2.5)	5.2	4.4	2.3	1.3
2	46 (5)	18.9	26.4	14.7	22.8
3+4	22 (4)	43.1	42.4	38.8	58.3
REM	19 (3)	13.5	18.9	19.0	15.3
Awake time	3.5 (1.5)	18.4	7.9	24.0	2.2
Movement time	0.3 (0.1)	0.4	0	0.8	0
Time lost	0	0.4	0	0.2	0

REM = rapid eye movement. * Growth hormone 6 mg administered.

defect (Zachmann, 1978). A hypothalamic lesion in the present patient was suggested by the delayed TSH response to TRH, hyperprolactinaemia and sleep stage abnormalities.

The initial phase of SWS is associated with GH release (Takahashi, Kipnis and Daughaday, 1968) and the total percentage SWS time decreases with age (Petre-Quadens, 1972). The increase in SWS time in the absence of a nocturnal rise in GH in the present patient is similar to the neuro-endocrine effects following the administration of the serotonin antagonist cyproheptidine to normal subjects (Dammacco *et al.*, 1977), suggesting a role for serotonergic neurones in the genesis of the disease. An acute feedback effect on these neurones is suggested by the increase in SWS time following GH administration. The decrement in stage 2 is a reflection of the large increase in SWS. The factors controlling the total REM time were uninvolved in the disease.

The rise of 10 points in i.q. over 5 years and the present abnormally high total SWS time may reflect a delay in cortical maturation caused by GH deficiency which is now poorly responsive to replacement therapy.

References

- DAMMACCO, F., PUCA, F.M., RIGILLO, N., GENCO, S., SPECCHIO, L.M., CHETRI, G., TORELLI, C., MASTRANGELO, C., CANDELIERE, C. & GALEONE, D. (1977) Inhibitory effect of cyproheptidine administration on the sleep-related growth hormone secretion in man. *Hormone and Metabolic Research*, **9**, 244.
- HALL, R., ORMSTON, B.J., BESSER, G.M., CRYER, R.J. & MCKENDRICK, M. (1972) The thyrotrophin-releasing hormone test in diseases of the pituitary and hypothalamus. *Lancet*, **i**, 759.
- PETRE-QUADENS, O. (1972) Sleep in mental retardation. In: *Sleep and the Maturing Nervous System*. (Ed. by Clemente, C.D., Purpura, D.P., Mayer, F.E.) p. 385-387. Academic Press, London and New York.
- RECHTSCHAFFEN, A. & KALES, A. (1968) A manual of standardized terminology, techniques and scoring system for sleep stages in human subjects. N.I.H. Publication No. 204, U.S. Government Printing Office, Washington D.C.
- SAVAGE, D.C.L., SWIFT, P.G.F., JOHNSTON, P.G.B., GOLDIE, D.J. & MURPHY, D. (1978) Combined test of anterior pituitary function in children. *Archives of Disease in Childhood*, **53**, 301.
- STOIAN, D., POENARU, S., STANESCU, V. & STEFANICA-MOTOC, L. (1969) EEG study of hypophyseal dwarfism. *Electroencephalography and Clinical Neurophysiology*, **27**, 635.
- SURWILLO, W.W. (1978) The electroencephalogram in a case of pituitary dwarfism before and after eight years of treatment with human growth hormone. *Developmental Neuroscience*, **1**, 62.
- TAKAHASHI, Y., KIPNIS, D. & DAUGHADAY, W.H. (1968) Growth hormone secretion during sleep. *Journal of Clinical Investigation*, **47**, 2079.
- TANNER, J.M., WHITEHOUSE, R.H. & TAKAISHI, M. (1966) Standards from birth to maturity for height, weight, height velocity and weight velocity: British Children, 1965. Part II. *Archives of Disease in Childhood*, **41**, 613.
- ZACHMANN, M. (1978) In: *Paediatrics and Growth*. (Ed. by Bartrop, D. Fellowship of Postgraduate Medicine, London). Report of the Fifth Unigate Paediatric Workshop. p. 121-129.