Endocrine Journal 1999, **46** (1), 227–230

NOTE

The 4A Syndrome Association with Osteoporosis

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Abstract. 4A syndrome is characterised by adrenocortical insufficiency, achalasia, alacrima, autonomic and other neurological abnormalities. We report an 18-year-old boy with 4 A syndrome and having all classical features of the disease including sensorimotor neuropathy. In addition, the patient had low aldosterone levels and signs of osteoporosis, which apparently developed without glucocorticoid replacement therapy. Although it is speculated that the lack of local growth factors, nutritional deficiency secondary to achalasia or receptor abnormalities regarding bone metabolism contribute to osteoporosis, its etiopathogenesis still needs to be clarified.

Key words: Allgrove syndrome, 4A syndrome, Osteoporosis, Sensorimotor neuropathy, Triple A syndrome

(*Endocrine Journal* **46**: 227–230, 1999)

FAMILIAL glucocorticoid deficiency associated with achalasia of the cardia and deficient tear production was described in 1978 by Allgrove *et al.* [1]. Since then a number of similar cases have been reported in the literature [2–11]. Triple A syndrome; characterised by adrenal insufficiency, achalasia and alacrima, is a rare disorder. Only 61 families with 92 patients have so far been described. Motor and sensory neuropathy have also been described, indicating that the disorder has a wide spectrum of clinical manifestations [10, 12, 13]. 4A syndrome (including autonomic neuropathy to triple A syndrome) was first described by Gazarian *et al.* in 1995 [14]. It is now well established that, in addition to motor and sensory neuropathy, autonomic neuropathy is a significant component of this syndrome [6, 8, 10, 13–15].

The various features that have been reported in Allgrove syndrome include short stature [6, 9], hyperkeratosis [1, 10, 11] delayed wound healing [1], velo-pharyngeal incompetence [8] and unusual facies [8].

The disorder is usually inherited in an autosomal recessive pattern and it has been shown to be associated with a GTP binding protein-linked hormone receptor mutation [16].

We present an 18-year-old white male with alacrima, achalasia, adrenocortical insufficiency, neurologic abnormalities and a not well-known feature, osteoporosis (Fig. 1).

Case Report

An 18-year-old white male admitted to the gastroenterology outpatient clinic of, suffering from dysphagia which started 6 months previously. A diagnosis of achalasia was made on the basis of characteristic abnormalities of the barium swallow oesophagogram and oesophageal manometry tracings. He later underwent successful pneumatic dilatation of the lower oesophageal sphincter. Six months after the first hospitalisation, the patient was readmitted to the gastroenterology clinic for

Received: July 28, 1998
Accepted: December 26, 1998
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recurrence of dysphagia.

There was no family history of any adrenal or oesophageal disorder, or lacrimation or neurological abnormalities. There is one healthy sibling. His weight was 44 kg (< 5th percentile), height was 165 cm (5th percentile), pulse was 100/min and blood pressure was 90/60 mmHg. The patient was malnourished and darkly pigmented, with particular darkening of the elbows, knees, nipples, palmar creases and buccal mucosa. There was bilateral pes cavus and flexion contractor in his hands. Schirmer test revealed alacrima. Neurological examination revealed sensorimotor neuropathy. According to WAIS-R findings his total IQ score was 91. His sexual maturity was associated with Tanner stage 5 and his bone age was associated with 17 years old.

Thyroid, renal and hepatic function tests, serum FSH, LH, PRL, GH, free and total testosterone levels were all within normal limits. Serum basal cortisol level was 41.38 nmol/L (N: 193.1–689.8 nmol/L), DHEAS level was 0.08 μmol/L (2.17–14.97 μmol/L), in the upright position the aldosterone level was 69.35 pmol/L (N: 110–860 pmol/L) and renin level was 0.3 ng/L (N: 0.5–1.0 ng/L) and the ACTH level was high at 155.2 pmol/L (N: 2.2–15.4 pmol/L). The fasting glucose level was 3.5 mmol/*l* (68 mg/d*l*). A short ACTH stimulation test (1 mg b-1–24 corticotrophin) was performed and there was no increase detected. The basal cortisol level was 41.38 nmol/L (1.5 μg/d*l*) and after ACTH stimulation, at 30, 60 and 90 min, the cortisol level was not changed (41.38 nmol/L). The peak GH response to L-Dopa stimulation was normal (11 μg/L). Electomyographic and nerve conduction studies indicated a sensorimotor neuropathy in the lower extremities.

Bone mineral content (BMC) and bone mineral density (BMD) was assessed by dual X-ray absorptiometry (Hologic QDR 4500-A). BMD and BMC scores are shown in Table 1. Serum calcium, phosphate, magnesium and 24 h urinary calcium levels were all in normal range; respectively 2.3 mmol/L, 1.3 mmol/L, 1 mmol/L and 210 mg/d. Serum bone alkaline phosphatase (Alkphase B, Metra Biosystems Inc, Mountain View, USA), procollagen (Prolagen C, Metra Biosystems Inc, Mountain View, USA) and urine pyridoline (Pyrilinks D, Metra Biosystems Inc, Mountain View, USA) concentrations were measured by enzyme linked immunosorbent assay. The serum PTH level was measured by RIA for intact PTH (Diagnostic System Laboratories Inc, Texas, USA). The serum bone alkaline phosphatase level was 7 U/L (11.6–30.6 U/L), urine pyridinoline level was 22.8 (N: 12.8–25.6) nM/mM creatinine, serum procollagen level was 76 ng/m*l* (N: 76-163 ng/m*l*), osteocalcin level was 31.7 ng/m*l* (N: 10–84 ng/m*l*) and PTH level was 46 pg/m*l* (N: 10–65 pg/m*l*).



Fig. 1. Patient's facial appearance was typical for 4A syndrome. Like most of the other affected patients he had a long, thin face with a long philtrum, narrow upper lip, and a down turned mouth.

Discussion

Allgrove syndrome is characterised by the appearance of isolated glucocorticoid deficiency, alacrima and achalasia. Although the association of achalasia and adrenal abnormalities has not yet been explained, the possibility of this being a degenerative process affecting both the adrenal glands and autonomic nerve structures has been considered. Associated features may include autonomic or peripheral neuropathy [10, 13], delayed wound healing [1], short stature, ataxia, optic atrophy [6] or mental retardation.

Alacrima, which appears to be the most

consistent early finding in Allgrove syndrome, is most likely a manifestation of an underlying autonomic neuropathy. A similar neuropathic process presumably underlies the oesophageal dysmotility and impaired bladder function. Radionuclide methods are being increasingly used to study gastric and bladder emptying and by these means disorders of autonomic neuropathy can be shown [17]. Assessing gastric and bladder emptying is valuable in the diagnosis of autonomic neuropathy and performing one of them, provides information on the other [18]. It was found that in normal subjects mean $t_{1/2}$ for bladder emptying was 23.24 ± 1.8 sec [18]. This patient's $t_{1/2}$ for bladder emptying was 34 sec. After all the secondary causes were excluded this prolongation was attributed to autonomic neuropathy. Low renin levels may also be attributable to autonomic dysfunction.

Glucococorticoid receptors are ubiquitous and glucocorticoid action varies from cell to cell. In *in-vitro* studies, glucocorticoids suppress or increase osteoblast proliferation depending on the state of maturation of the cells and the species [19, 20]. In culture studies, glucocorticoids have two additional effects: they increase sensitivity to parathyroid hormone and stimulate osteoblastic differentiation. Glucocorticoids were shown to increase the number of PTH receptors as well as the abundance of G proteins, which mediate PTH stimulation of adenylate cyclase [21]. The effect of glucocorticoids on the expression of osteoblastic features could reflect the requirement of this hormone for osteoblast differentiation. Glucocorticoids were shown to increase the expression of alkaline phosphatase in osteoblastic tumour cells [22].

Table 1. BMC and BMD data of the patient

	BMC (gm)	BMD (gm/cm^2)	T score
L1	9.17	0.659	−3.17
L2	10.65	0.767	−2.97
L3	12.49	0.708	−3.59
L4	12.87	0.682	−4.21
L1–L4	45.19	0.703	−3.53
Neck	3.57	0.641	−3.00
Trochanter	6.21	0.541	−2.33
Intertrochanteric area	13.97	0.782	−3.07
Ward's triangle	23.75	0.577	−2.12

Although glucocorticoid effects on bone were examined *in vitro*, there is no evidence of osteoporosis *in vivo* with glucocorticoid deficiency.

His bone mass was found to be lower than the controls (Table 1). Osteoporosis is not a well-known feature of 4A syndrome, there being only one report in the literature [15]. It has been thought that protein malnutrition secondary to achalasia might be responsible for his osteoporosis. Osteomalacia due to vitamin D deficiency may also be indicated, but he had no characteristic clinical findings for osteomalacia and serum calcium, phosphate, PTH and 24 h urinary calcium levels were all within normal limits. It is still very speculative to explain the pathogenesis of osteoporosis by nutritional factors. Lack of local growth factors and the receptor abnormality regarding bone metabolism might be the further contributing factors. In conclusion, we think that osteoporosis accompanying 4A syndrome is still an interesting clinical observation. Osteoporosis in 4A syndrome demands further explanation and research.

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