

# Neurological and adrenal dysfunction in the adrenal insufficiency/alacrima/achalasia (3A) syndrome

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## Abstract

**Review of 20 patients with glucocorticoid deficiency (three cases also with salt loss) associated with absent tear secretion (19 cases) and achalasia of the cardia (15 cases) revealed neurological abnormalities in 17 including hyper-reflexia, muscle weakness, dysarthria, and ataxia together with impaired intelligence and abnormal autonomic function, particularly postural hypotension. These findings indicate that significant neurological problems are common in this multisystem disorder.**

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Familial glucocorticoid deficiency associated with achalasia of the cardia and deficient tear production was described in 1978 by Allgrove *et al.*<sup>1</sup> Since then there have been a number of reports of similar cases.<sup>2-5</sup> More recent reports indicate that there may be impairment of autonomic function in the condition<sup>6,7</sup> and motor and sensory neuropathy have also been described,<sup>8,9</sup> together with ataxia, optic atrophy and impaired intelligence,<sup>10,11</sup> indicating that the disorder has a wide spectrum of clinical manifestations. This paper describes the findings in a multicentre collaborative study carried out to ascertain the incidence of disordered neurological and automatic function in the syndrome.

## Methods

In order to obtain information on patients with the adrenal insufficiency/alacrima/achalasia syndrome in the UK, questionnaires were sent to 39 senior members of the British Society for Paediatric Endocrinology asking for information on any cases under their care. Thirty seven questionnaires were returned, and six cases with the disorder were identified in the UK (cases 4, 5, 6, 13, 15, 17 described below).

To increase the number of patients available for study, members of the European Society for Paediatric Endocrinology known to have had patients with the disorder under their care were invited to participate in the study and were sent questionnaires asking for information on the presence of adrenal insufficiency, alacrima, achalasia of the cardia, abnormal neurological findings, tests of autonomic function, evidence of intellectual impairment, skin manifestations, and family history.

In some families siblings have died in early infancy, probably as a result of adrenal insufficiency. These have not been included in the

study as little information is available on their neurological status.

## Results

Twenty patients (13 males, seven females) aged from 2.5 to 29.0 years at last follow up were identified. Their clinical details are summarised in the table. All have evidence of impaired cortisol secretion. Fourteen also have both alacrima that has been present from early infancy and achalasia of the cardia. Six patients have incomplete forms of the syndrome. Five have alacrima without achalasia (cases 16, 17, 18, 19, 20) and one has achalasia but normal tear secretion (case 7).

Earlier findings in 11 of the patients have been published previously.<sup>12-17</sup>

## ADRENAL INSUFFICIENCY

### Cortisol deficiency

Evidence of cortisol deficiency was present in all cases (table) and was diagnosed between the ages of 1.8 and 10.0 years on the basis of an absent plasma cortisol response to 1-24 corticotrophin (ACTH) (14 cases), absence of a rise in urinary cortisol metabolites after ACTH stimulation (one case), persistently low unstimulated concentrations of plasma cortisol (one case), and/or marked increase of plasma ACTH (14 cases). At the time of diagnosis four of these latter patients showed a significant rise in plasma cortisol after injection of 1-24 ACTH.

The age at which symptoms of adrenal insufficiency began ranged from 1.0 to 8.3 years. In 16 cases the initial symptoms were related to recurrent hypoglycaemia, usually associated with increased skin pigmentation. Two patients presented with vomiting (cases 9, 15). In two cases, both with affected siblings, there were no symptoms of cortisol deficiency (cases 6, 16). When restudied 9.2 years later at the age of 13.7 years one of these patients (case 6) still had a significant rise in plasma cortisol after injection of 1-24 ACTH but plasma ACTH remained raised.

With one exception, all the patients have been treated with oral hydrocortisone and have remained free from further episodes of hypoglycaemia. In one patient who had no symptoms (case 16) the parents refused to allow steroid replacement therapy.

### Aldosterone deficiency

Three patients showed evidence of salt loss at the time of diagnosis. In one (case 14) plasma sodium

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## Clinical findings in 20 patients with the 3A syndrome

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Reference to previous publication		12	13	1, 17		1, 17	16	15	16	15	15					15		15		
Sex	M	F	F	M	M	M	F	M	M	F	M	M	M	M	M	F	F	M	M	F
Age last seen (years)	29	25	23	23	22	20	17	17	16	13	12	12	11	9	9	6	5	4	2	2
Cortisol deficiency	+	+	+	+	+	L	+	+	+	+	+	+	+	+	+	L	+	+	+	+
Salt loss	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-
Alacrima	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Achalasia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+
<i>Neurological dysfunction</i>																				
Hyper-reflexia	+	+	+	+	+	+	+	-	+	+	-	-	+	+	-	-	+	+	+	-
Increased tone	+	+	-	-	-	-	+	+	+	+	+	-	-	-	-	-	+	+	+	-
Muscle weakness/wasting	+	-	-	+	+	-	+	-	+	-	+	-	+	+	-	-	+	+	-	-
Extensor plantar responses	+	+	-	+	+	+	+	-	+	-	-	+	-	-	-	-	-	-	+	-
Dysarthria/nasal speech	-	+	+	+	+	-	+	-	+	+	+	-	-	-	-	-	-	+	-	-
Ataxia/clumsiness	-	-	-	-	-	-	+	+	+	+	+	+	-	-	-	-	-	-	-	-
Sensory impairment	-	-	-	+	+	+	-	-	-	+	-	-	+	-	-	-	-	-	-	-
<i>Autonomic dysfunction</i>																				
Postural hypotension	-	-	-	+	+	+	+	+	-	+	+	-	-	-	-	-	+	-	-	-
Unequal pupils	-	-	-	-	-	-	+	+	-	-	-	-	-	+	-	+	-	-	+	-
Absent/reduced sweating	-	+	-	+	NT	NT	NT	-	-	+	+	-	-	-	-	-	-	-	-	-
Abnormal heart reflexes	NT	NT	NT	+	-	+	+	-	-	-	-	NT	NT	NT	-	-	+	-	-	-
Abnormal methacholine test	NT	NT	NT	+	NT	+	NT	NT	NT	NT	NT	NT	+	NT	-	NT	+	NT	NT	NT
Abnormal histamine test	NT	NT	NT	-	NT	+	NT	NT	NT	NT	NT	-	+	NT	-	NT	NT	NT	NT	NT
<i>Mental retardation</i>																				
Mental retardation	+	+	+	+	+	-	+	-	+	+	+	-	SLD	-	-	-	+	-	-	-
<i>Skin changes</i>																				
Fissured palms	-	-	-	+	-	+	-	+	+	+	+	+	+	+	-	-	+	+	-	-
Cutis anserina	-	-	-	-	-	+	+	+	+	+	+	+	+	-	-	-	+	+	+	-

Present = +, absent = -; NT = not tested; SLD = specific learning deficit; L = latent.

concentration was 132 mmol/l and potassium 6.0 mmol/l. In the second (case 15), plasma sodium was 123 mmol/l, urine sodium 62 mmol/l, and plasma renin activity was markedly increased. In the third (case 17) plasma sodium fell to 128 mmol/l and plasma renin activity rose to an abnormally high value after four days on a low sodium diet. All three patients have been treated with 9 $\alpha$ -fludrocortisone and have shown a satisfactory response.

## ALACRIMA

Nineteen patients have had alacrima since early infancy and most have required 'artificial tears' to avoid discomfort. Only one patient has apparently normal tear secretion (case 7).

## ACHALASIA OF THE CARDIA

Fifteen patients have achalasia of the cardia, diagnosed between the ages of 2.5 and 17.0 years (table). In four cases (7, 8, 10, 11) the diagnosis of achalasia was made 1.0 to 4.3 years before the diagnosis of cortisol deficiency. There is considerable variation in the ages at which symptoms of achalasia were first noted, ranging from 0.5 to 16.0 years. Eleven patients have required one or more surgical procedures (Heller's operation), two have been treated by dilatation, and two have been managed with medical treatment.

Of the five cases without achalasia (table), one is a 6.7 year old girl (case 16) who had an older brother with alacrima and cortisol deficiency who first developed symptoms of achalasia at the age of 6.0 years. This girl also has 'latent' cortisol deficiency and is not on steroid therapy. The other four cases without achalasia are aged 2.6 to 5.5 years.

## NEUROLOGICAL FINDINGS

Seventeen patients are considered to have evidence of neurological impairment (table),

often with a mixed pattern of upper and lower motor neurone dysfunction. The most common findings were of hyper-reflexia (15 cases), increased limb tone (10 cases), extensor plantar responses (nine cases), and muscle weakness and/or wasting (nine cases). Dysarthria/nasal speech (eight patients), ataxia or clumsiness (six patients), and sensory impairment (five patients) were also recorded as were optic atrophy (cases 3 and 5), nerve deafness (case 12), and recurrent seizures (case 2). The ages at which these abnormal findings were first noted ranged from 2.4 to 15.5 years (median age 10.0 years). In general, abnormal neurological findings were more common in the older patients, and the three cases with no abnormalities were aged 2, 6, and 9 years, respectively. In the older patients the neurological disorder appeared to be either very slowly progressive or static at their last review.

## NERVE CONDUCTION STUDIES

Nerve conduction studies were carried out in 11 patients (table); evidence of denervation was present in six.

## AUTONOMICAL DISTURBANCE

Impaired autonomic function was a feature in 11 patients (table). Postural hypotension was present in eight cases, inequality of the pupils in five, absent or reduced sweating in four, and impotence in one (case 5). Of the 14 cases who had evaluation of their cardiac reflexes, four had abnormal results. The dermal flare response to histamine was assessed in only five patients and was abnormal in two. Methacholine tests were carried out in five cases; four were abnormal.

## IMPAIRED INTELLECT

Eleven patients have some degree of intellectual impairment. Six of the seven patients who have

had formal tests of psychometric function have IQ scores between 68 and 84 and one patient with an above average IQ score (113) has specific learning disabilities and is making poor progress at school. Three of the patients who have not had formal IQ tests have been unable to attend normal school because of moderate retardation and the fourth is making poor progress at school. The remaining nine patients are considered to be of normal intelligence but none has had a formal psychometric assessment.

#### SKIN CHANGES

Skin abnormalities are present in 12 patients. Ten have hyperkeratosis of the palms of their hands with multiple fine fissures, and eight have cutis anserina (table).

#### OTHER FEATURES

One patient has had multiple nasal polyps (case 1), one has scoliosis (case 12), and one cleft palate (case 19).

#### FAMILY HISTORY

There are three pairs of siblings in the present study (cases 4 and 6, 8 and 16, and 10 and 11). Seven further siblings (four males, three females) have died in early childhood, probably as a result of adrenal insufficiency. Seventeen siblings (seven males, 10 females) are alive and well with no clinical features of the syndrome.

None of the parents are consanguineous or show features of the disorder. However, a maternal great grandmother and maternal grandfather of case 1 had alacrima and skin pigmentation but were otherwise healthy.

#### Discussion

As would be expected in view of the method of case ascertainment, all the patients in this study show evidence of impaired cortisol secretion, and their clinical features are very similar to those described in other conditions associated with cortisol deficiency. Hypoglycaemia – often associated with Addisonian skin pigmentation – was usually the presenting symptom, starting before the age of 5 years in most cases and almost invariably before the age of 10 years.

At the time of diagnosis, four children appeared to have incomplete cortisol deficiency, as there was a significant rise in plasma cortisol after 1–24 ACTH stimulation. In these patients the diagnosis of cortisol deficiency was based on the presence of abnormally raised concentrations of endogenous ACTH. In one of these subjects (case 6) there was still a cortisol response to 1–24 ACTH when he was retested at the age of 13 years, suggesting that persistent incomplete cortisol deficiency can occur in the disorder. However, Moore *et al* noted progressive loss of cortisol secretion in one of their patients between the ages of 23 and 29 years,<sup>11</sup> and complete glucocorticoid deficiency may eventually develop in our patient.

While most of our patients appear to have isolated cortisol deficiency, three also have

evidence of aldosterone deficiency. These findings are in keeping with previously published results in other patients with this disorder that indicate that most have normal mineralocorticoid function but that salt loss may be present in some cases.<sup>2</sup>

The relationship between the adrenal disorder in our patients and those with classical 'ACTH unresponsiveness' who have isolated glucocorticoid deficiency<sup>18,19</sup> is uncertain. However, both conditions are probably inherited as autosomal recessive disorders and cause progressive (and usually selective) loss of cortisol secretion in early childhood.<sup>20</sup>

The high incidence of enteric neurological abnormality in our patients is very striking. Achalasia of the cardia, diagnosed between the ages of 2 and 17 years, was present in 15. As in most of the other published cases, the diagnosis was usually made after – or at the same time – as that of cortisol deficiency. However, in four cases the diagnosis of achalasia preceded the diagnosis of cortisol deficiency by one to four years. Five of our patients do not currently have any evidence of achalasia but one of them has an older sibling with the disorder and the others are still less than 6 years old. It remains to be seen whether they will go on to develop achalasia.

In a series of 35 children with achalasia of the cardia Nihoul-Fékété *et al* found only one with alacrima and cortisol deficiency,<sup>21</sup> indicating that most children with achalasia have normal adrenal function. However, our results emphasise the importance of checking cortisol secretion if achalasia is associated with absent tear secretion or any of the neurological features described above.

The relationship between our patients and other cases of familial achalasia and alacrima with normal cortisol secretion<sup>22–24</sup> is uncertain, as is the relationship with familial achalasia associated with mental retardation and microcephaly.<sup>25</sup> However, in these latter syndromes neurological and autonomic impairment have not been described, and they may represent different entities.

In the present study abnormalities of the nervous system were often associated with impaired intellect. In most of our patients the neurological findings were first recorded at the time of diagnosis of cortisol deficiency or some years later, usually after the onset of achalasia. While this suggests that central neurological disorder might be a relatively late manifestation in the 3A syndrome, it is possible that the more subtle neurological features were not detected in early childhood.

The nature of the abnormal neurological features described above is of interest as they indicate that both central and peripheral neurones may be affected, and the findings are similar to those in subacute combined degeneration of the cord.<sup>17</sup> The natural history of this neurological dysfunction is still not completely clear but our experience suggests that it is slowly progressive but may become static in adult life. Abnormalities of autonomic function were also common in our patients. The most disabling symptom was that of postural hypotension but in one subject impotence was a source of distress.

As there are many known similarities between

the enteric and central nervous systems<sup>26</sup> it seems very likely that the alacrima, autonomic dysfunction, and abnormalities of the central nervous system have an origin in common with the achalasia that is caused by a denervating process affecting primarily the myenteric plexus.<sup>27</sup>

Our observations indicate that the 3A syndrome may also be associated with changes in the skin. Ten of the patients have mild hyperkeratosis of the palms with large numbers of fine fissures and eight have 'cutis anserina'.

Several of our patients have siblings with the disorder, some of whom died in early infancy before detailed investigation could be carried out. This finding, and the relatively even sex ratio, support the view that the disorder is transmitted by autosomal recessive inheritance. It is possible that all the features of the 3A syndrome are due to deletion of autosomal DNA with loss of closely linked genes necessary for normal adrenocortical and neural function, and dermal keratinisation. Alternatively, both the neurological and adrenal pathology could be the result of an as yet undetermined metabolic error, or the adrenal failure could be related to degeneration of its autonomic nerve supply.

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