Endocrinopathies in paediatric-onset neuromyelitis optica spectrum disorder with aquaporin 4 (AQP4) antibody

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Abstract

The involvement of the diencephalic regions in neuromyelitis optica spectrum disorder (NMOSD) may lead to endocrinopathies. In this study we identified the following endocrinopathies in 60%(15/25) of young people with paediatric-onset AQP4-Ab NMOSD: morbid obesity (n=8), hyperinsulinaemia (n=5), hyperandrogenism (n=5), amenorrhoea (n=5), hyponatraemia (n=4), short stature (n=3) and central hypothyroidism (n=2) irrespective of hypothalamic lesions. Morbid obesity was seen in 88%(7/8) of children of Caribbean origin. As endocrinopathies, were prevalent in the majority of paediatric-onset AQP4-Ab NMOSD, endocrine surveillance and in particular early aggressive weight management is required for patients with AQP4-Ab NMOSD.

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Introduction

The revised diagnostic criteria for neuromyelitis optica spectrum disorders (NMOSD) are considered to be appropriate for paediatric patients[1]. NMOSD-typical brain lesions may involve the diencephalic regions, including the hypothalamus, and the periependymal regions in the brainstem[1], with consequent clinical symptoms. In particular, endocrinopathies and disorders of water balance, associated with CNS Aquaporin 4 (AQP4) autoimmunity, have been attributed to hypothalamic involvement.[2]

An association between recurrent inflammation of the optic nerves and spinal cord with endocrinopathies was first described in 1997 in patients with the distinct clinical syndrome known as recurrent optic neuromyelitis (RONM); this was prior to the discovery of AQP4-Antibody (Ab). RONM was predominantly described in Afro-Caribbean and African-Brazilian women with recurrent CNS demyelination associated with endocrinopathies, such as central hypothyroidism, hyperphagia with obesity and diabetes mellitus[3-5]. The patients described with RONM would fulfil the current diagnostic criteria for neuromyelitis optica NMOSD[1], even in the absence of AQP4-Ab. In view of the phenotypic overlap in patients with NMOSD and RONM, we aimed to investigate whether endocrinopathies are seen in paediatric onset AQP4-Ab positive NMOSD patients.

Patients and methods

Clinical, demographic and treatment data were collected from 25 consecutive paediatric-onset (under the age of 18 years) AQP4-Ab positive NMOSD patients, according to the recent diagnostic criteria[1], seen in the nationally commissioned Oxford NMO service (NRES ref. 10/H0606/56). All patients had undergone brain and spinal cord imaging according to local MRI protocols. Endocrinological tests were only carried out when clinically indicated. Morbid obesity was defined as BMI>40 and short stature was defined as height < 2SD below the mean height for age and sex. Hyperinsulinaemia was defined as HOMA-IR >1.5 or insulin peak >100 mU/l to oral glucose load. Amenorrhoea was defined as absence of periods by 16 years (primary) or absence of 3 consecutive periods in a woman with previously normal (monthly) cycles(secondary). Polycystic ovary syndrome was defined as An LH/FSH ratio of greater than 2.5:1. Central hypothyroidism was defined as low free T4/3 in the presence of a normal or low TSH. Statistical analysis was performed using commercially available software GraphPad Prism 6 [GraphPad Software Inc]). Non-parametric statistical tests (Mann-Whitney tests) were used for continuous distributions, and Fisher's exact tests for nominal data. Parental consent was obtained for publication of relevant clinical information.

Results

The clinical and radiological features of all AQP4-Ab positive NMOSD patients are summarized in **table 1**.

A total of 15 patients (60%) had symptoms of endocrinopathies. These included: morbid obesity (n=8), hyperinsulinaemia (n=5), hyperandrogenism (n=5), secondary amenorrhoea (n=5), hyponatraemia (n=4), short stature (n=3) and central hypothyroidism (n=2).

When comparing patients with endocrinopathies to those without, there was no difference in the patients' demographics, clinical presentations at onset and relapse, or cumulative dose of steroids received (Table 1). Patients with endocrinopathies were more likely to have abnormal brain MRI 12/15 than those without endocrinopathies during the course of their illness (12/15 vs 3/10 p=0.034), but there was no difference in hypothalamic involvement on imaging between patients with and those without endocrinopathies (4/15 vs 1/10, p=0.61). Morbid obesity was seen in 7/8 (87.5%) of children of Caribbean origin and only in one child (1/17, 5.9%) of non-Caribbean origin (p=0.002). Growth charts and neuroimaging of three female patients with morbid obesity are illustrated in **Figure 1**.

Discussion

In this cohort of paediatric onset AQP4-Ab NMOSD, we have identified endocrinopathies in 60% of the patients, contributing to significant morbidity with potential effect on the patients' quality of life and long-term health.

It is possible that in some patients the endocrinopathies result from symptomatic hypothalamic lesions resulting in dysregulation of the homeostatic control of energy balance, which leads to metabolic alterations and obesity.[6] In the original description of RNMO with endocrinopathies both enhancing and non-enhancing hypothalamic MRI lesions were observed in several patients. In addition inflammatory lesions were observed in hypothalamic area in one patient at pathological level[3,4]. Interestingly, no difference, in terms of evident of hypothalamic involvement, at the time of study, between patients with endocrinopathies and those without were observed in our cohort. This is in keeping with previous paediatric case reports of hypothalamic–pituitary axis dysfunction in children with NMOSD occurring with[7] or without[8] radiological evidence of hypothalamic inflammation. As not all patients were imaged with 3T MRI and it is possible that low field MRI could explain this discrepancy. More advance imaging techniques may detect microscopic tissue abnormalities suggestive of active inflammation or evidence of previous lesions in the hypothalamus

Hyperinsulinaemia was only seen in patients with obesity and it is possibly a consequence of the obesity. Hyperandrogenism with polycystic ovary syndrome and secondary amenorrhoea were seen in 5/25 (20%) of the patients; three with obesity and two with normal BMI. A previous study of paediatric NMOSD described 3 (out of 9) patients with irregular menstrual cycles before their initial attack, which became regular when patients were commenced on treatment[9]. In the same study catamenial exacerbation of disease occurred in one patient, and initiating oral contraceptives corresponded with

decreased attacks. Hyponatraemia, secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) was reported in 4/25 (16%) patients, all at presentation, which resolved with treatment, in keeping with recent reports of SIADH in 6/41 (15%) of adult patients with AQP4-Ab NMOSD[10].

Six of 15 (40%) patients with endocrinopathies in our cohort were of African-Caribbean origin. Although some of these features, in particularly the obesity, were initially attributed to the use of steroids, the patients continued to gain weight (>100kg addition in 2 patients over 2 and 3 years respectively) after steroids were stopped (**Figure 1**). It is possible that the exogenous corticosteroids may induce epigenetic changes in the glucocorticoid receptors resulting in chronic increases in hypothalamic corticosterone levels and consequent obesity and hyperphagia, as recently reported in an animal model[11]. Although obesity is common in British women of African-Caribbean origin, there is no straightforward relationship between obesity and ethnicity, with a complex interplay of factors that subsequently contribute to nutrition-related diseases.

A major limitation of this study is the lack of standardised endocrinological assessment in the patients for hypothalamic-pituitary axis dysfunction throughout the disease course. Furthermore, it is likely that some of the features, such as the obesity, are multifactorial making it difficult to disentangle in this small cohort. Nevertheless, the striking finding of endocrinopathies in 60% in children with AQP4-Ab NMOSD, with morbid obesity in 86% of affected children of Caribbean origin should argue for endocrine surveillance and mandate early aggressive weight management in all patients with AQP4-Ab NMOSD.

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Table 1: Comparison of clinical and paraclinical features in AQP4-Ab positive patients with and without endocrinopathies.

	Endocrinopathies (n=15)	No endocrinopathies (n=10)	P value
Age of disease onset (median, IQR)	12 (8-14)	11 (8-15.5)	0.80
Female	14 (93%)	10 (100%)	1.0
Ethnicity			
Caucasian	5 (33%)	6 (60%)	0.24
Afro-Caribbean	6 (40%)	1 (10%)	0.18
Asian	4 (27%)	2 (20%)	1.0
Other	0 (0%)	1 (10%)	0.4
Disease course			
Optic nerve	7 (47%)	7 (70%)	0.41
Cerebrum	7 (47%)	1 (10%)	0.088
Brainstem	13 (87%)	5 (50%)	0.075
Spinal cord	10 (67%)	7 (70%)	1.0
Magnetic resonance imaging			
Abnormal Brain	12 (80%)	3 (30%)	0.034
Hypothalamic involvement	4 (27%)	1 (10%)	0.61
Expanded Disability Status Scale (median, IQR)	2 (1.5-3)	2.5 (1-4)	0.59
Maintenance treatment	14 (93%)	8 (80%)	0.54
Maintenance oral prednisolone (>3months)	7 (47%, 1 obese patient)	7 (70%)	0.41
Rituximab	5 (33%)	0 (0%)	0.06
Azathioprine/ Mycophenolate mofetil	11 (73%)	7 (70%)	1.0

Figure 1: Growth charts of the three female patients with NMOSD and morbid obesity. Hypothalamic lesions on MRI were reported in patients 1 and 3 but not in patient 2. Patient 1 first presented with an area postrema syndrome at the age of 12 years. Her weight on presentation was 63kg (BMI 21). She was referred to endocrinology service at age 12.5 years due to concerns about her weight (BMI 36.7 +3.5 SDS). She was not on steroids. She was noted to have striae, acanthosis nigricans and mild acne but no other Cushingoid features. She was also oligomenorrhoeic. Basal endocrine testing was normal. A subsequent oral glucose tolerance test performed at age 12.6 years showed a impaired fasting glucose (6.2 mmol/l), impaired glucose tolerance (9.0 mmol/l) and a peak insulin concentration that was above the upper limit of detection of >300 mU/l. She was subsequently started on metformin in escalating doses. At the age of 13.2 years, due to continued oligomenorrhoea, a pelvic ultrasound was performed which showed polycystic ovaries. However, despite dietary advice, at the age of 14 years her weight has increased to 162kg (**BMI 55, > + 4SDS**). **Patient 2** first presented with area postrema syndrome at the age of 10 years. Her weight on presentation was 43.5kg (BMI 21.9). She was seen by the endocrinology service at age 12.0 years. She was menarchal. She was noted to be obese (BMI 27.6, +2.7 SDS) with some hirsutism, and subsequently developed striae and acanthosis nigricans, and was noted to be Cushingoid. Baseline endocrine testing revealed central hypothyroidism (free T4 6.8 pmol/l (normal range 10.8-19.0), free T3 5.9 pmol/l (normal range 6.2-9.5), TSH 1.5 mU/l (normal <6.0)) and marked insulin resistance (fasting glucose 5.2 mmol/l, fasting insulin 75.3 mU/l, HOMA-IR 17.3). Her endocrine status was otherwise normal. She was subsequently started on levothyroxine supplementation and metformin. Despite rapidly increasing doses of levothyroxine and metformin, her weight continued to escalate, a pelvic ultrasound at the age of 13.5 years revealed polycystic ovaries, although she was still experiencing regular periods. After prednisolone was stopped her BMI decreased to 44.4 from a peak of 49.8(+4.1 to +3.9 SDS). However, despite dietary advice and increasing her levothyroxine and metformin to maximum doses, she continued to gain weight. At the age of 15.5 years and a **BMI of 46.9 (+4.0 SDS)**, she was referred for bariatric surgery. **Patient 3** first presented with encephalopathy at the age of 10 years. Neuroimaging revealed signal changes through amygdala, temporal lobes hypothalamus and dorsal medulla and an longitudinally extensive transverse myelitis At the time of admission her weight was 56kg (BMI 22). At the age of 12.7 years, patient 3's escalating obesity (BMI 35.5, +3.4 SDS) led to an endocrinology review where she was found to be in late puberty (Tanner stage 4) but had not attained menarche. Baseline endocrine function was normal. Her weight continued to escalate despite continued efforts at dietary restriction and lifestyle changes, and at 13.1 years her **BMI was 42.5 (+3.8 SDS**). Examination revealed significant striae and Cushingoid features but spontaneous onset of menarche. Sequential trials of metformin and orlistat were instituted, but both caused significant side effects (abdominal pain and headaches) and were subsequently stopped. At the age of 13years, her prednisolone was weaned and stopped. In combination with dietary restriction, this led to a degree of weight loss and at last follow-up she had lost 9.5 kg.

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Authors' contribution

YH study concept and design, acquisition of data, analysis and interpretation; critical revision of the manuscript for important intellectual content. SM, HWG, SW, PF, EW, ML acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. SC, MIL acquisition of data, critical revision of the manuscript for important intellectual content. AV, OC analysis and interpretation, critical revision of the manuscript for important intellectual content. JC, CH analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision

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