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Regular Article

Clinical and biochemical assessment of depressive symptoms in patients with Alkaptonuria before and after two years of treatment with nitisinone

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ABSTRACT

Objective: Concerns exist over hypertyrosinaemia that is observed following treatment with nitisinone. It has been suggested that tyrosine may compete with tryptophan for uptake into the central nervous system, and or inhibit tryptophan hydroxylase activity reducing serotonin production. At the National Alkaptonuria (AKU) Centre nitisinone is being used off-licence to treat AKU, and there is uncertainty over whether hypertyrosinaemia may alter mood. Herein results from clinical and biochemical assessments of depression in patients with AKU before and after treatment with nitisinone are presented.

Patients and methods: 63 patients were included pre-nitisinone treatment, of these 39 and 32 patients were followed up 12 and 24 months after treatment. All patients had Becks Depression Inventory-II (BDI-II) assessments (scores can range from 0 to 63, the higher the score the more severe the category of depression), and where possible urinary monoamine neurotransmitter metabolites and serum aromatic amino acids were measured as biochemical markers of depression.

Results: Mean (± standard deviation) BDI-II scores pre-nitisinone, and after 12 and 24 months were 10.1(9.6); 9.8(10.0) and 10.5(9.9) ($p \geq 0.05$, all visits). Paired scores ($n = 32$), showed a significant increase at 24 months compared to baseline 10.5(9.9) vs. 8.6 (7.8) ($p = 0.03$). Serum tyrosine increased at least 6-fold following nitisinone ($p \leq 0.0001$, all visits), and urinary 3-methoxytyramine (3-MT) increased at 12 and 24 months ($p \leq 0.0001$), and 5-hydroxyindole acetic acid (5-HIAA) decreased at 12 months ($p = 0.03$).

Conclusions: BDI-II scores were significantly higher following 24 months of nitisinone therapy in patients that were followed up, however the majority of these patients remained in the minimal category of depression. Serum tyrosine and urinary 3-MT increased significantly following treatment with nitisinone. In contrast urinary 5-HIAA did not decrease consistently over the same period studied. Together these findings suggest nitisinone does not cause depression despite some observed effects on monoamine neurotransmitter metabolism.

1. Introduction

Alkaptonuria (AKU, OMIM: 203500) is a rare autosomal recessive disorder of the tyrosine metabolic pathway, occurring 1 in 250,000 of the general population [25]. It results from a congenital deficiency in the enzyme homogentisate-1,2-dioxygenase (HGD, E.C.1.12.11.5). One of the major biochemical consequences of AKU is that the circulating concentration of homogentisic acid (HGA) significantly increases despite significant renal excretion. It is proposed that circulating HGA is responsible for a number of the complications which are observed, for a detailed review see Ranganath et al. [27]. The psychological impact of this painful and debilitating musculoskeletal disease has never been reported. Katon et al. [17] reported that patients with chronic medical illness, such as diabetes, stroke, cancer and heart disease have a high prevalence of major depressive illness.

Assessing patients' psychological state before and after treatment is

Abbreviations: AKU, Alkaptonuria; HGA, homogentisic acid; HGD, homogentisate-1,2-dioxygenase; HPPD, hydroxyphenylpyruvic acid dioxygenase; HT1, tyrosinaemia type 1; NAC, National Alkaptonuria Centre; BDI-II, Beck's depression inventory-II; NMA, normetadrenaline; MA, metadrenaline; 3-MT, 3-methoxytyramine; 5-HIAA, 5-hydroxyindole acetic acid

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important as judgements can be made about whether treatment will result in a change in mood or depression. This is highly relevant when considering patients with AKU that are being treated with nitisinone, a competitive inhibitor of hydroxyphenylpyruvic acid dioxygenase (HPPD, E.C. 1.13.11.27). This is because its use results in marked hypertyrosinaemia [4, 15, 22, 24, 28, 31]. This has also been reported in patients with Hereditary Tyrosinaemia type-1 (HT I, OMIM 276700) treated with nitisinone [16, 20, 21, 33, 34].

The metabolic fate of these supraphysiological tyrosine concentrations is unknown. It has been reported that it can cause corneal keratopathy [18]. In addition it is known that tyrosine is the precursor for the biosynthesis of the neurotransmitter dopamine, which plays a role in mood.

In HT1 it is estimated that 35% of children have neurodevelopmental delay [21]. Several mechanisms have been postulated, including: increased transport of tyrosine into the brain; decreased transport of other neutral amino acids into the brain (specifically tryptophan, the precursor of serotonin); increased central nervous system dopamine; decreased central nervous system serotonin, oxidative damage from δ-aminolevulinic acid and succinylacetone (the toxic metabolites in HT 1) or modification of neuronal proteins [12, 13, 32]. It has also been suggested that altered serotonin metabolism may be due to direct inhibition of tryptophan hydroxylase (TPH; EC 1.14.16.4) activity by tyrosine, which leads to a reduced biosynthesis of serotonin [32].

Due to the possibility that hypertyrosinaemia may have an impact on neurodevelopment in HT1, concerns exist around it's off licence use in patients with AKU. Therapy is currently commenced when patients are ≥16 years old so they are less likely to suffer the same neurodevelopmental delay. Therefore the focus is on whether changes in neurotransmitter metabolism may affect mood and result in depression.

The impact of hypertyrosinaemia on neurotransmitter metabolism in patients with AKU following nitisinone therapy has been previously reported [4]. Catecholamine neurotransmitter metabolites 3-methoxytyramine (3-MT) (dopamine metabolite) and normetadrenaline (NMA) (noradrenaline metabolite) were shown to increase and decrease significantly following nitisinone therapy, respectively. The urinary serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) was shown to decrease following nitisinone therapy, but the decrease was only significant at the highest daily dose of 8 mg. These biochemical data were however limited in that this was a short term dosing study that did not report any psychometric data, and serum tryptophan and phenylalanine concentrations were not reported.

Herein for the first time we report BDI-II scores as a self-reporting measure of depression [1, 2] in patients with AKU, pre-nitisinone and at 12 and 24 months nitisinone therapy. In addition urinary monoamine metabolites of catecholamine and serotonin neurotransmitters and associated serum aromatic amino acids tyrosine, phenylalanine and tryptophan are reported in a sub-group of patients.

2. Patients and analytical methods

2.1. Patients

2.1.1. Protocol for patients that attend the National Alkaptonuria Centre (NAC) for treatment with nitisinone

The protocol for treatment at the NAC is that patients with confirmed AKU are commenced on a 2 mg dose of nitisinone, on alternative days for the first three months, which is then increased to 2 mg daily thereafter. Assessments are repeated on an annual basis to monitor response to therapy.

Inclusion criteria for treatment with nitisinone are that individuals must have the diagnosis of AKU; must be a resident of England or Scotland, and be over the age of 16 years. Confirmed diagnosis of AKU is based upon increased urinary HGA excretion [urine HGA in healthy volunteers has been demonstrated in the order of < 2.91 μmol/day [3]] and mandatory for referral to the NAC. Exclusion criteria are individuals must not be pregnant and or lactating. Nitisinone is used in an off-licence setting to investigate its safety and efficacy in the treatment of this rare disease. All patients are provided with written information about the scope of the centre and the assessments they will receive. All patients at the NAC have biochemical measurements and clinical assessments are performed at baseline, day four (two days post-nitisinone), three months, six months and 12 months; with annual monitoring thereafter.

2.2. Ethical approval

Data collection and analyses at the NAC has approval from the Royal Liverpool and Broadgreen University Hospital Trusts Audit Committee (Audit no. ACO3836). As data were collected as part of the clinical service ethical approval was not required. Data is obtained following standard clinical assessments upon referral to the NAC. Patients are informed verbally and through patient information leaflets about the activities of the NAC. Patients are also explicitly informed that data may be used for publication and within the NAC patient information leaflet.

2.3. Subjects included in the study

Sixty-three patients [26 female, mean age (± standard deviation) 51.3(16.8) years (range 18–75); 37 male, mean age 47.6(13.9) years (range 16–70)] were included at baseline in this 24 month longitudinal survey reporting the BDI-II data.

BDI-II data were also included at 12 (n = 39) and 24 (n = 32) months following 2 mg daily nitisinone. Twenty-four and 31 patients of the 63 patients included at baseline were not included at 12 and 24 months, respectively. Five patients were excluded as they were not resident of England or Scotland. The remaining 19 and 26 patients did not have follow-up visits at 12 and 24 months respectively, either because they did not attend or because they had not attended the NAC for long enough for follow-up visits at the point of data collection.

Twenty-four hour urine samples for measurement of monoamine metabolites were collected into 2.5 L bottles containing 30 mL of 5 N H_2SO_4; aliquots were stored away from bright light at −20 °C. Urine samples were from baseline (pre-nitisinone), three months (2 mg nitisinone every other day), six months (2 mg nitisinone daily), 12 months (2 mg nitisinone daily) and 24 months (2 mg nitisinone daily). No patients included in this study had renal impairment (eGFR > 60 mL/min/1.73m^2 in all cases). Completeness of 24 h urine collection was assessed by measurement of urine creatinine (Roche Diagnostics, Germany) and all patients had urine creatinine concentrations within the normal reference range (9.0–18.0 μmol/24 h, in house reference range).

Serum samples (S-monovette, Sarstedt, Germany) were collected from patients at the same visits as urine samples. Samples were centrifuged (10 min at 3000 rpm) and stored at −20 °C until analysis. All serum samples were collected following an overnight fast (at least 8 h). Patients' dietary intake of protein was managed through a 7 day food diary by a combination of lower protein in diet and phenylalanine/tyrosine free meal exchanges.

2.4. Methods

2.4.1. Beck's depression inventory-II

BDI-II [1, 2] is a self-scored questionnaire that includes 21 items; each has four alternative statements ranked in order of severity from zero to three. The questionnaire evaluates a number of emotions including: mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, insomnia, and loss of appetite. Conventional cut-offs are 0–13 for minimal depression, 14–19 for mild depression,