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Serum uric acid levels in optic neuritis

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Uric acid, an antioxidant, is reduced in multiple sclerosis (MS). Patients with gout have a reduced incidence of MS. Optic neuritis (ON), often the first manifestation of MS, is not known to be associated with reduced uric acid. Patients with recent onset of ON were investigated to determine whether uric acid levels were reduced at presentation. Twenty-one patients with ON were included, 17 females and 4 males. The mean (SD) serum uric acid in the ON female group was 184.4 (±55.1) μmol/L (range, 116–309 μmol/L), whilst in the control group it was 235.2 (±50.2) μmol/L (range, 172–381 μmol/L). The difference was statistically significant ($\chi^2 = 8.93$, $P = 0.003$). In the small male cohort, mean (SD) serum uric acid was 305 (±52.1) μmol/L, whilst in the control group it was 328 (±80.4) μmol/L. These differences were not statistically significant. Reduced antioxidant reserve is possibly an early pathogenic mechanism in inflammatory demyelination, and raises the possibility that low uric acid levels could be an indicator of disease activity. Since optic neuropathies of other causes were not investigated, future research needs to determine whether low uric acid represents a unique feature of optic neuritis or is seen in other optic neuropathies.
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Introduction

Optic neuritis (ON) is an inflammatory demyelinating condition affecting the optic nerve. It occurs in isolation or as part of multiple sclerosis (MS), where it represents the first manifestation in a substantial proportion of cases. Isolated ON is considered by many to be a forme fruste of MS.[1]

Reactive oxygen and nitrogen species and in particular peroxynitrite play a major role in the inflammation and demyelination of MS.[2] Uric acid, a natural antioxidant, is a powerful inhibitor of peroxynitrite.[2] Studies have found reduced serum uric acid levels in established MS[2,3] and patients with gout (hyperuricemia), have significantly reduced incidence of MS.[2] Moreover, treatments that increase this natural antioxidant can be beneficial in MS.[4,5] Because ON is often the first manifestation of MS, possibly before destructive processes are well established, we investigated the serum uric acid in patients with ON.

Patients and methods

Patients attending the Eye Casualty at the Leicester Royal Infirmary with clinical features of ON, who were referred and agreed to participate, were included in our study. Inclusion criteria were largely based on the Optic Neuritis Treatment Trial,[6] with some modifications. Patients with a first attack of ON were included if aged between 18 and 45 years. Older patients with established MS or who had previous ON were also included (Table 1). A history of unilateral sudden loss of vision, a relative afferent pupillary defect (RAPD) and defect on Humphrey visual field screening were required for inclusion. Snellen visual acuity was measured. Colour vision was assessed on Ishihara plates. The optic disc and macula were assessed by dilated funduscopy. Systemic causes of inflammatory optic neuropathy such as SLE, sarcoidosis or syphilis were ruled out. Serum uric acid was measured by an enzymatic colorimetric assay using the Aeroset system.

Patients were scheduled for a magnetic resonance imaging (MRI) scan within 30 days of presentation. Serum uric acid levels were obtained from a control group of age- and sex-matched individuals. ON patients and control subjects completed a diet questionnaire including average weekly meat and alcohol consumption. The study had local ethical committee approval.

Results

Twenty-one patients with confirmed ON were included in the study, 17 females and 4 males, mean (SD) age 33.3 (±7.4) years (range, 20–47). The clinical details and uric acid levels are shown in Table 1. The mean (SD) age for females was 34 (±8.04) years (range, 20–47). The mean (SD) male age was 30.2 (±1.89) years (range 29–33).

The mean (SD) serum uric acid in the ON female group was 184.4 (±55.1) μmol/L; (range, 116–309 μmol/L). The

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Table 1 Showing patient data

Patient	*Age (years)*	*Sex*	*Race*	*MRI result*	*Uric acid (μmol/L)*	*Medical history*	*Ocular pain*	*Optic disc appearance*
1	42	F	CA	Demyelination	**166**	MS	Y	Normal
2	24	F	CA	Demyelination	**136**	Asthma	Y	R palor
3	31	F	CA	Demyelination	**167**	Nil	Y	R palor
4	36	F	CA	Demyelination	309	Nil	Y	R palor
5	36	F	CA	Normal	228	Asthma	Y	L swollen
6	24	F	CA	Normal	**185**	Nil	N	R swollen
7	47	F	CA	Demyelination	**176**	Hysterectomy, ON	Y	Normal
8	45	F	CA	Normal	**162**	Nil	Y	Normal
9	31	F	CA	Demyelination	**149**	MS, ON	Y	Normal
10	20	F	CA	Demyelination	215	Nil	N	R swollen
11	36	F	CA	Demyelination	**185**	Migraine, MS, ON	N	L swollen
12	29	F	A	Demyelination	**152**	Nil	N	Normal
13	27	F	CA	Demyelination	245	Asthma	N	R swollen
14	37	F	CA	Demyelination	**142**	Migraine, IBS	Y	Normal
15	45	F	A	Demyelination	**118**	Nil	Y	Normal
16	39	F	AfC	No scan	**116**	Fibroids	Y	Normal
17	29	F	CA	No scan	283	IBS	Y	R swollen
18	30	M	CA	Demyelination	**233**	Nil	Y	Normal
19	33	M	CA	Demyelination	310	Nil	Y	L swollen
20	29	M	CA	Demyelination	357	MS	N	Normal
21	29	M	CA	Demyelination	320	MS, ON	Y	R swollen

Uric acid: Low results in bold
F: female, M: male, CA: Caucasian, A: Asian (from the Indian subcontinent), AfC: Afro-Caribbean, IBS: irritable bowel syndrome

mean (SD) level in the control female group ($n = 22$) was 235.2 ($\pm$50.2) μmol/L; (range, 172–381) ($P = 0.006$), with a mean (SD) age of 33.27 ($\pm$8.28) years (range 20–48). In 12 of the 17 female patients (70.6%) levels were below the normal laboratory range (200–360 μmol/L). Five of 22 control females (22.7%) had uric acid levels below the lower limit of normal and one (4.5%) above the upper limit. The difference between the proportion of female ON and control female patients with low uric acid was statistically significant ($\chi^2 = 8.93$, $P = 0.003$).

In the small male cohort, mean (SD) serum uric acid level was 305 ($\pm$52.1) μmol/L. One of the four patients (25%) had a value below the normal range (260–500 μmol/L). The male control group ($n = 16$) had a mean (SD) uric acid level of 328 ($\pm$80.4) μmol/L (range, 168–471). The mean (SD) age was 32.31 ($\pm$4.27) years (range 22–38). Two of 16 controls (12.5%) had a uric acid value below the lower limit of normal. The differences in the male cohort were not statistically significant.

For the whole ON group (males and females), 13 of 21 (61.9%) uric acid levels were below the lower limit of normal compared to 7 of 38 (18.4%) in the age- and sex-matched control group ($\chi^2 = 11.4$, $P = 0.001$). The differences in uric acid between the whole ON and control groups were statistically significant (mean (SD) 207 ($\pm$72) μmol/L for ON; 274 ($\pm$72) μmol/L for controls; $P = 0.002$). Nineteen of the 21 patients in the study underwent MRI, which revealed at least one demyelinating lesion in 16 patients (84.2%). Three were reported as normal. Two patients failed to attend for MRI.

Five patients with ON had the diagnosis of MS and one patient had experienced an episode of ON. Two of these patients had normal serum uric acid. The others had low serum uric acid. In this small group, the proportion of patients with uric acid under the lower limit of normal (67%) was significantly higher than in controls ($\chi^2 = 5.8$; $P = 0.015$) although the mean levels of uric acid were not significantly different from control levels ($P > 0.05$). Of 15 patients with ON as a first clinically isolated syndrome, 10 (67%) had uric acid levels below the lower limit of normal ($\chi^2 = 11.5$, $P = 0.001$ versus control group); also, the mean uric acid levels were significantly lower than in the controls ($P = 0.004$).

None of the 21 patients in the study were taking medication known to affect serum uric acid levels.[7,8] All patients had normal renal function.

There were no differences in the average alcohol consumption or diet between ON and control subjects.

Discussion

We found that overall, ON patients had lower serum uric acid levels than age- and sex-matched control subjects. A highly significant proportion of ON patients had uric acid levels below the lower limit of the normal range. These results were also obtained when the female cohort was investigated separately. The group of males with ON was small, only four patients, therefore no solid conclusion can be drawn about uric acid in ON in males. However, the results suggest, as shown in MS,[3,9] that the female gender contributes significantly to the difference between ON patients and control subjects. The relatively high

proportion of normal subjects with uric acid levels below normal in this study may be explained by the younger mean age of the control group than that of the general population generating normative data, as uric acid increases with age.[10] Nevertheless the proportion was significantly lower than age-matched patients with ON.

This is the first report of an association between ON and depressed uric acid.

Uric acid, a naturally occurring antioxidant, is the end-product of purine metabolism. Studies in MS have revealed reduced serum uric acid levels. In the animal model of MS, experimental autoimmune encephalomyelitis (EAE) in mice, uric acid treatment prevents or delays development of symptoms and can improve established disease.[2]

However, treatment of MS with uric acid is difficult, as bacterial uricase in the gastrointestinal tract destroys it. Inosine, the precursor, is, however, readily absorbed and has been used to the treat EAE.[11] In humans, a small group of ten chronic and acute MS patients have been treated with inosine with encouraging preliminary results.[4]

This is the first study investigating uric acid in clinically isolated demyelinating syndromes. Previous studies in MS have found moderately reduced uric acid in remission and more significantly reduced uric acid levels in relapses of MS.[3,9] Interestingly, in this study, even in those with ON as a clinically isolated demyelinating syndrome, the uric acid level is very low. In fact, the decrease in uric acid appeared to be more prominent in ON as a clinically isolated syndrome. This finding suggests that a decreased antioxidant reserve is an early pathogenic mechanism in inflammatory demyelination. Moreover, this study raises the possibility of low uric acid levels being used as an indicator of disease activity. Since optic neuropathies of other causes were not investigated, future research needs to determine whether low uric acid levels represent a unique feature of optic neuritis or whether they are seen in optic neuropathies of other causes.

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