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Chapter

The Link between Hypouricemia and Neurodegenerative Disorders

Anna Mihailova, Maximiliane Trapp and Natalija Kakurina

Abstract

The potential danger to patients' health due to hypouricemia has only recently become a research topic of interest. While it has been established that normal uric acid levels have antioxidative and neuroprotective properties, the loss of these functions with uric acid levels below the normal range have been studied only recently and findings suggest potential detrimental effects on the brain and cognitive abilities. The purpose of this study is to look at potential connections between hypouricemia and neurodegenerative disorders such as Alzheimer's disease and vascular dementia. Seventy-seven inpatients and outpatients with routine uric acid testing were included and further stratified into patients with neurodegenerative disease and patients without neurodegenerative disease. The results showed that rates of Alzheimer's disease differ between patients with hypouricemia and normal uric acid levels, however this association was not found for patients with vascular dementia. This provides evidence for potential effects of hypouricemia and raises the question for further research define a safe range of serum uric acid.

Keywords: uric acid, hypouricemia, neurodegenerative diseases, Alzheimer's disease, vascular dementia

1. Introduction

The effects of hyperuricemia on the cardiovascular system have been extensively studied and it is widely known that hyperuricemia is regarded as a risk factor for cardiovascular disease such as hypertension. Hypouricemia, on the other hand, had been mostly disregarded in research until recently when researchers started to investigate potential sequela from below normal uric acid levels. This was mostly due to the advent of newer and more effective urate lowering medication that it raised the question whether lowering uric acid below normal levels could have any clinical significance.

1.1 The uric acid paradox

Uric acid had been studied in the vitro where it was established that normal levels have oxidative properties that are pro-inflammatory within cells and antioxidative and neuroprotective effects by reducing oxidative stress within plasma to which the discovering researchers referred to as the oxidative-antioxidative paradox. This aligns

with the findings that hyperuricemia can have an inflammatory response causing pathologies such as gout and cardiovascular disease through endothelial dysfunction while hypouricemia could have potential effects on the neurovascular system by the loss of the antioxidative and neuroprotective properties. And indeed, recent suggest exactly this finding that there could be a possible association between low serum uric acid levels and the development of neurodegenerative diseases. Researchers are now interested in finding evidence that preventing uric acid levels to fall below the normal range could ultimately prevent neurodegenerative diseases and if so, what would a safe range of uric acid levels be.

This work embraces a review of articles and recent research on hypouricemia that had been published between November 1980 until November 2019 and investigates a patient group with neurodegenerative disease and a patient group without such a disease for possible differences. The aim was to explore a possible relationship between subnormal uric acid levels and neurodegenerative disease among patients in Latvia.

2. Uric acid and its function

Uric acid is an end product from the degradation of the purine nucleosides, adenosine and guanosine. In mammals, uricase breaks uric acid further down to allantoin which is then excreted in urine [1]. Humans lack this enzyme, leaving uric acid as the end product. This has led researchers to take a closer look at the function of uric acid. In 1981 one of the leading articles was published by Ames et el. in which they stated that have found evidence that uric acid has the ability to function as a powerful antioxidant by scavenging single oxygens and radicals and at physiological levels has further protective properties on erythrocytes that are comparable with ascorbate [2]. These findings about urate's antioxidative function were again confirmed in 2008 by Sautin and Johnson but the researchers added that uric acid can be pro-inflammatory through oxidative properties. Interestingly, they discovered that uric acid can have execute different effects in different parts of the body. In plasma, uric acid functions as an antioxidant and within cells as a pro-oxidant which led them to refer to this contradiction as the oxidant-antioxidant paradox [3]. This paradox explains that hyperuricemia can lead to an inflammatory response causing gout, endothelial dysfunction causing cardiovascular diseases [4] and it can act as a neuroprotector via the antioxidant capacity of uric acid and subsequent reduction of oxidative damage. On the other hand, low uric acid levels have been shown to decrease the activity of myeloperoxidase and increase lipid peroxidation through the loss of the antioxidant properties of uric acid [5]. The reduced antioxidant capacity is believed to be neurotoxic due to increased oxidative damage [6] but it remains unclear if this loss is sufficient to induce neurodegenerative diseases [7].

2.1 Mortality and serum uric acid levels

There has been a long history of research focusing on the effects of hyperuricemia and its clinical significance. If uric acid levels exceed the baseline the pro-oxidative effect causes damage to the tissue which can induce disease. As an example, hyperuricemia has been widely accepted as an independent risk factor for hypertension due to the inflammatory response by urate that can lead to endothelial dysfunction, however hyperuricemia remains controversial whether it is an independent risk factor

for cardiovascular disease. In 2006, the Rotterdam study claimed that hyperuricemia is a risk factor for cardiovascular disease and stroke [8] while this claim was refuted in 2016 by Kuwabara who states that there are too many cofounders to establish this association [9]. Another pathology that has hyperuricemia as a risk factor, is gout. This inflammatory arthritis occurs when serum urate levels are saturated that monosodium urate crystals form and deposit in the joints leading to intense pain and discomfort. The most commonly prescribed treatment for gout prevention is urate lowering medication such as allopurinol while for acute flares non-steroidal anti-inflammatory drugs are used. When using urate lowering medication, the current guidelines and their respective uric acid levels become of interest. In the current European guidelines for the treatment of gout, it is recommended that uric acid levels should be less than 6 mg/dL but not less than 3 mg/dL [10]. It is noteworthy that the lower threshold has been established due to the lack of improvement for gout rather than the potential sequela of hypouricemia.

The mortality from high and from low uric acid has been investigated by several studies. One example is the EPOCH-Japan study which is a large-scale review of 13 cohort studies in Japan. The results showed that low uric acid levels have an increased overall mortality from cardiovascular diseases. They concluded a J- or U-shaped association between low and high uric acid levels and cardiovascular mortality [11]. Another study conducted in Korea also confirms a U-shaped, independent relationship between serum uric acid level and mortality [12]. The relationship between mortality and hyperuricemia can be explained by the activation of the NLRP3 inflammasome and a resulting increase of Interleukin-1ß and increased production of ROS [13] which then trigger arteriosclerosis [9]. However, how exactly hypouricemia is associated with mortality has not been fully understood as of now. Possible explanations given by the authors of the Korean study were malnutrition, side effects of medications that affect urate levels, other comorbidities, and increased risk of oxidative stress due to a reduction in the antioxidative properties of uric acid.

2.2 Causes of hypouricemia

The definition for hypouricemia is serum urate levels less than 2 mg/dL [14]. The causes can be either through inherited disorders that decrease the uric production such as hereditary xanthinuria or purine nucleosidase phosphorylase deficiency or disorders that increase the urinary excretion of urate such as inherited familial renal hypouricemia or acquired disorders such as Fanconi syndrome. More commonly, however, is hypouricemia through a secondary process such a urate lowering medication which are commonly used in the management of gout or uric acid oxidation with derivatives of uricase that are commonly used in oncology.

2.3 Inherited hypouricemia

To study the effects of hypouricemia, researchers have been focusing on patients with cases of inherited low uric acid. For these patients, it has been established that the low uric acid levels are not due to another disease or condition that influences serum uric acid level and therefore, patients with inherited low uric acid make an ideal model to study the possible risks of urate-lowering therapies without a lower threshold. In theory that sounds very promising, however inherited defects causing

decreased uric acid production are very rare and often are incidental findings. Familial renal hypouricemia, a genetic condition causing increased excretion of uric acid through a loss of function mutation in the renal tubular urate transporter, is among the most commonly studied condition and while its prevalence worldwide is unknown, it has been established that it is more common in Asian countries such as Japan (prevalence: 0.3%) [15] and South Korea (prevalence: 1.39%) [16]. Two types of familial renal hypouricemia have been defined: for renal hypouricemia type 1 the mutation is in the SLC22A12 gene (URAT1 transporter) while the mutation for renal hypouricemia type 2 is in the SLC2A9 gene (GLUT9). Most commonly patients remain asymptomatic with these mutations, however both types have been linked to cases of nephrolithiasis and exercise-induced acute kidney injury (EIAKI) while renal hypouricemia type 2 has additionally been linked to a more severe condition, the posterior reversible encephalopathy syndrome (PRES), which presents with headache, seizures, and other neurological findings. In 2012, a case report by Fujinaga et al. was published in the European Journal of Pediatrics about a child with familial renal hypouricemia type 1 and PRES. In the case report they suggest that PRES is not due to severe hypouricemia per se, but rather an adverse effect of severe EIAKI [17]. For further understanding on how renal hypouricemia can cause posterior reversible encephalopathy syndrome more research is needed.

2.4 Acquired hypouricemia

By far the most common cause of acquired hypouricemia is due to the use of urate-lowering therapies and subsequent decreased uric acid production [18]. These therapies are most commonly used in the treatment of gout which is a disease characterized by abnormal uric acid crystal formation and deposition due to elevated plasma uric acid levels. Deposits of uric acid crystals are commonly referred to as a tophus or tophi. For the control of clinically significant gout flares, urate lowering therapy such as xanthine oxidase inhibitors and recombinant uricase or uricosuric agents are prescribed. Recombinant uricase and uricosuric agents are typically used in more severe cases. In most guidelines the recommendation is to lower plasma urate below 6 mg/dL. If tophi are present guidelines suggest to further lower plasma urate below 5 mg/dL [10, 19–23]. There are only two guidelines, the British Society for Rheumatology [20] and EULAR recommendation [10] that mention potential outcomes from lowering urate levels. It is believed that low urate levels increase the risk for neurodegenerative disorders [24] such as Parkinson's disease, Alzheimer's disease and Amyotrophic lateral sclerosis and elevated levels may have a protective function [6, 25]. Furthermore, in the past decade the results of seven randomized clinical trials have been published that investigated potential dangers of urate-lowering therapy by the three most commonly used therapies (Xanthine oxidase inhibitors, recombinant uricase and uricosuric agents) [26–32]. In the largest trial, the CARES study, a statistically significant relationship between intensive urate lowering therapy and mortality was found [32]. In the other trials this relationship was not statistically significant but mortality was highest in the arms with the greatest urate lowering effect, raising the suspicion of safety concerns with commonly used gout medication without a lower cut-off threshold [33]. To date only EULAR recommendations suggest a specific threshold, in this case not lower than 3 mg/dL. Other than EULAR and the British Society for Rheumatology [10, 20], no major published guidelines currently address the potential dangers of lowering urate levels beyond the normal range.

2.5 Adverse effects of hypouricemia

There is still little conclusive evidence about the specific short- and long-term clinical effects of hypouricemia, despite the fact that several research have shown a general relationship between mortality and both hyper- and hypouricemia. A theoretical concern as no cases (except for patients with tumor lysis syndrome) have been reported to date [34], is the possible risk from using urate-lowering medication with xanthine oxidase inhibitors that could lead to hypoxanthine and xanthine build up that then consequently could potentially cause xanthine nephropathy. Emerging research established that the physiologic function of normal serum uric acid acts as a protective antioxidant and the subsequent loss of this function when levels are below normal, however research has not been able to establish a definite relationship and only suspects a link between hypouricemia and the development of neurodegenerative disease.

3. Methodology

3.1 Study subjects

The following study was completed as an observational study in the period of September to December of 2019 at following four hospitals and clinics in Latvia: Daugavpils Regional Hospital, Orto Clinic, Riga East University Hospital and Pauls Stradins Clinical University Hospital. The patient selection was randomized of both inpatient and outpatient patients, whose serum uric acid was measured as part of their routine blood test. The criteria of exclusion were based on pathologies that could secondarily affect uric acid levels such as high creatinine and/or chronic kidney diseases, as well as patients receiving urate lowering medication and if the admission was related to a pathology directly affecting the patient's uric acid concentration. Lastly, patients who refused to allow their data to be used for research reasons were also not included in the study. Included patients were asked to sign a consent form and were interviewed regarding their age, height, weight and history of myocardial infarction or stroke (and at what age it occurred) and whether they have been diagnosed with a neurodegenerative disease. As a second step, the medical records were reviewed to confirm the patient's eligibility to be included in the research, as well as to confirm their medical history and information and to collect serum uric acid from the laboratory data. Lastly, the included patients were then stratified into two categories: patients with neurodegenerative disease and patients without neurodegenerative disease.

3.2 Variables

In accordance with the hospitals range of uric acid, hypouricemia was defined as less than 200 μmol/L and the most recent measurement of the routine blood testing was used for this research. Patients with elevated creatinine above 110 μmol/L were excluded from the study. Blood pressure measurements were performed once on the right arm. A large group of patients have had a history of hypertension and have been receiving anti-hypertensive treatment. The history of myocardial infarction or stroke was confirmed by review of the patient's medical chart. Neurodegenerative diseases of interest included Alzheimer's disease and vascular Dementia. Alzheimer's disease

was defined as G30 in the ICD-10 classification and vascular Dementia was defined as F01.5 in ICD-10 classification. The ICD-10 classification have been translated from the Latvian SKK klasifikācija.

3.3 Statistical analysis

Statistical analysis was performed using statistical software SPSS (*Statistical package for the social sciences*, SPSS Inc., Chicago, IL), Version 20, 2018. Demographic data were expressed as mean with standard deviations. The statistical analysis was performed in accordance with objectives using following statistical methods: Kolmogorov-Smirnov test, Pearson correlation coefficient, two tailed t-test for independent means, Fisher exact probability test and chi-squared test. Statistical significance was set at $\alpha = 0.05$.

4. Results

4.1 Demographics

In total 100 patients were asked for their consent to participate in this study of which five declined and 18 patients were ineligible due to the exclusion criteria. The remaining 77 patients were stratified into two groups: 45 patients with a neurodegenerative disease and 32 patients without a neurodegenerative disease. The group of patients with neurodegenerative disease included 4 patients with Alzheimer's disease (G30 in ICD-10 classification), 40 patients with vascular dementia (F01.5 in ICD-10 classification) and one patient with a dementia in other disease classified elsewhere (F02.8 in ICD-10 classification). The average serum uric acid levels for patients with a neurodegenerative disease was 387 ± 210 μmol/L compared to 409 ± 156 μmol/L in patients without a neurodegenerative disease. There were six patients with a neurodegenerative disease whose serum uric acid levels fall below the normal range of 200 μmol/L. Further details of the study population are depicted in **Table 1**.

4.2 Uric acid correlation with age and kidney function

The kidneys, whose function decreases with age, excrete two-thirds of uric acid from the body [35, 36]. Therefore, the correlation between serum uric acid concentration and GFR was calculated. As expected, there is a moderate positive correlation ($r = 0.58$) for patients for neurodegenerative disease and ($r = 0.51$) demonstrated in **Figure 1** and for patients without this diagnosis demonstrated in **Figure 2**. Both results are statistically significant at $p < 0.05$. Additionally, the correlation between serum uric acid concentration and age in the subject of interest was tested by Pearson correlation coefficient. Results showed that in both groups there is a weak correlation ($r = 0.0615$) for patients with neurodegenerative diseases and ($r = -0.70$) for patients without neurodegenerative disease and both are statistically not significant at $p < 0.05$.

4.3 Uric acid differences between patients with neurodegenerative disease and patients without neurodegenerative disease

The selection of patients occurred randomly and were immediately stratified into the two groups of patients with neurodegenerative disease and without

Variables	Patients with neurodegenerative disease	Patients without neurodegenerative disease
Females	26	23
Males	19	9
Age in years	81 ± 10	70 ± 13
Weight in kg	75.6 ± 11	80.3 ± 14
Height in cm	170 ± 7	167 ± 9
BMI	26.3 ± 11	28.8 ± 13
Uric acid in μmol/L	387 ± 210	409 ± 156
Creatinine in μmol/L	83 ± 26	76 ± 20
GFR in mL/min/1.73 m^2	98 ± 16	96 ± 14
Alzheimer's disease patients	4	NA
Vascular dementia patients	40	NA
Dementia in other diseases classified elsewhere	1	NA
Systolic blood pressure in mmHg	131 ± 18	122 ± 12
Diastolic blood pressure in mmHg	74 ± 10	79 ± 8
Myocardial infarction patients	0	5 (average age 73)
Single stroke episode patients	3 (average age 71)	3 (average age 60)

Table 1.
Demographics of the study population.

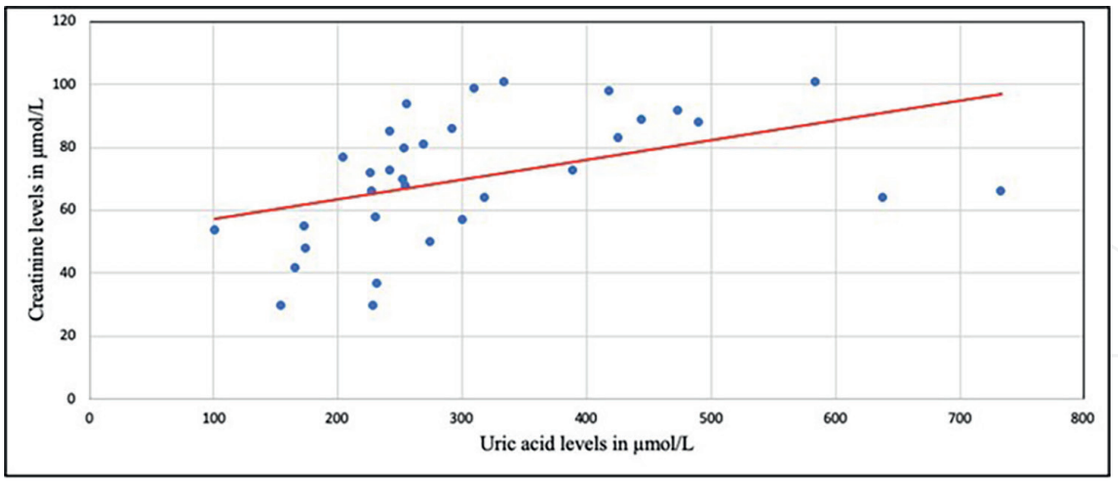

Figure 1.
Moderate positive correlation between uric acid levels and creatinine levels in patients with neurodegenerative disease.

neurodegenerative disease regardless of their uric acid levels. To investigate whether a difference of the uric acid levels exists between those two groups, a two tailed t-test for two independent means with a significance level $p < 0.05$ was used. The result was statistically not significant $t = -0.50$, $p = 0.62$, meaning that there is no difference in the uric acid concentrations within the two groups.

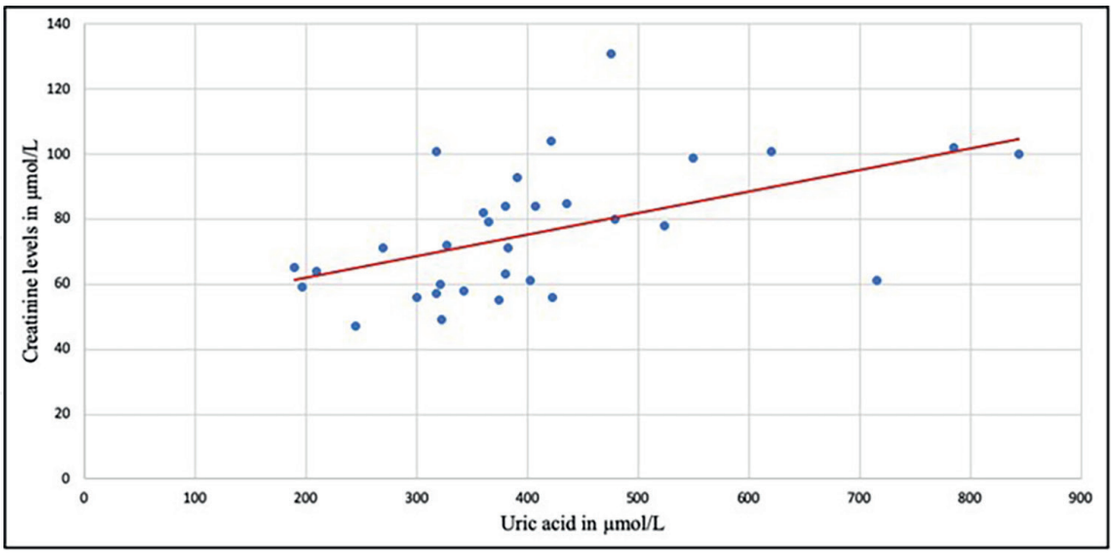

Figure 2.
Moderate positive correlation between uric acid levels and creatinine levels in patients without neurodegenerative disease.

4.4 Uric acid differences and its association with myocardial infarction and stroke

Whether hyperuricemia is a risk factor for cardiovascular has been controversial over the past decade and the most recent consensus was that there are too many confounders to claim hyperuricemia as an independent risk factor for cardiovascular disease. For the patient population in this research, the authors wanted to investigate whether there is a statistically significant association between serum uric acid levels and patient's history of myocardial infarcts and strokes. The stratified patient groups were tested for a statistically significant relationship between uric acid levels and myocardial infarction with a Fisher exact probability test. The result was statistically significant with a significance level $p < 0.05$. The same test was used to test for a statistically significant relationship between uric acid levels and stroke for which the result was statistically not significant $p = 0.69$. This means there is detectable association in both groups between uric acid levels in patients with myocardial infarction and patients without a myocardial infarction. However, this association cannot be found for patients with a single stroke episode.

4.5 Uric acid differences and its association with neurodegenerative diseases in stratified age groups

Both groups, the group of patients with a neurodegenerative disease and the group of patients without neurodegenerative disease, were then stratified into the age group 50–79 years and patients over the age of 80 due to the possible influence of increased age on vascular dementia. The average uric acid levels for the different age groups can be seen in **Figure 3**. The stratified group was tested with a Fisher exact probability test for a statistically significant relationship between the two age groups and the diagnosis of vascular dementia which was statistically significant with a significance level $p < 0.05$. If the same stratified group was tested for the statistically significant relationship of the age groups and Alzheimer's disease, the result was statistically not

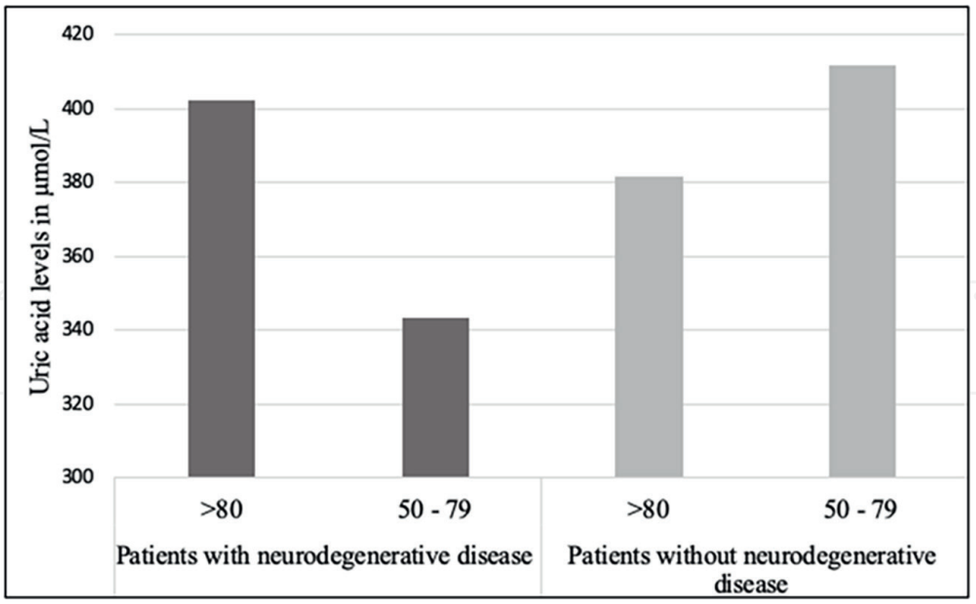

Figure 3.
Average uric acid levels in different age groups.

significant. Due to the statistically significant relationship between the stratified age groups and vascular dementia and the earlier result of our statistical analysis that showed a weak positive correlation between age and serum uric acid levels, the same stratified age groups were tested for their uric acid levels with a two tailed t-test for two independent means for a statistically significant difference. The result was not significant $t = -2.0$, $p = 0.07$.

4.6 Hypouricemia and its association with neurodegenerative diseases

The focus of interest of this study was the potential association between hypouricemia and neurodegenerative diseases. To investigate this potential relationship the first step was to explore how patients with hypouricemic levels compared to patients with normal uric acid levels for their rate in vascular dementia and for their rate in Alzheimer's disease. A chi-squared test of independence with a significance level $p < 0.05$ was used and showed a non-random association between the rate of vascular dementia in patients with hypouricemia and patients with normal serum uric acid levels. This finding was not statistically significant x^2 (1, N = 77) =0.56, $p = 0.45$ which indicates that there is no significant difference in the rate of vascular dementia regardless of the uric acid levels. The same test was used to investigate Alzheimer's disease and the results showed a non-random distribution that was statistically significant x^2 (1, N = 77) = 10.5, $p = 0.001$. Therefore, it can be concluded that there is a statistically significant difference of Alzheimer's disease in patients with hypouricemia and patients with normal uric acid.

5. Discussion

Uric acid has a complex function in the body. It can induce inflammation, endothelial dysfunction, and oxidative stress but it is also known to be a powerful antioxidant. This is known as the oxidant-antioxidant paradox. Laboratory studies

have shown that the loss of uric acid causes a reduction in antioxidant capacity. This is mediated by decreased myeloperoxidase activity and increased lipid peroxidation and subsequent oxidative damage. Research has shown that this oxidative damage can be linked to neurodegenerative diseases such as Parkinson's disease and Multiple Sclerosis [37].

The pathogenesis of Alzheimer's disease is characterized primarily by the accumulation of neurotoxic metabolic products and abnormal proteins such a beta amyloid and neurofibrillary tangles [38, 39]. This creates an environment hostile to normal brain cell function and results in progressive dysregulation and synaptic dysfunction. Several studies have implicated neuronal excitotoxicity from overstimulation of N-methyl-D-aspartate (NMDA) receptors [40]. These specific neurotoxic processes may be counteracted by neuroprotective factors in the brain, with the antioxidative effects of normal blood uric acid playing a significant role. In patients with hypouricemia the loss of this neuroprotective effect could exacerbate damage from excitoxic pathways and unchecked neuronal loss.

However, vascular dementia has showed conflicting results in recent research and does not appear to be related to lower uric acid levels. This does not come as a surprise, given the large number of risk factors and the multifactorial etiologies of vascular dementia. Even while certain neuroprotective variables could contribute to the development or severity of vascular dementia, the relative importance of these factors may be overwhelmed by the greater effects of cardiovascular, renal, and overall endothelial risk factors.

The positive result for the chi-squared test of independence in the rate of Alzheimer's disease between patients with hypouricemia and patients with normal serum uric acid levels gives weight to the neuroprotective hypothesis of normal serum uric acid levels, and the possible effects of its loss in patients with hypouricemia. Similarly, the negative result of the chi-square analysis in patients with vascular dementia provides some reinforcement to the idea that the multiple risk factors of vascular dementia may outweigh any potential neuroprotective effects of normal uric acid levels. Another possibility is that uric acid may have no role in vascular dementia given a statistically not significant result of the t-test indicated there is no association between the means of uric acid in stratified age groups with vascular dementia. Furthermore, the results of the Fisher exact probability tests showed that age is a definitive influence on vascular dementia, but it had no effect on the rate of Alzheimer's disease. Overall, these findings are consistent with previously published data that has indicated a potential neuroprotective effect of normal uric acid levels.

Analysis of this data set showed several other findings. Patients with neurodegenerative diseases did not have statistically significant different uric acid levels than those without such a diagnosis, however the small sample size of patients makes it challenging to interpret this one data point. Furthermore, the statistically significant result of the Fisher exact probability test of serum uric acid levels in the two patient groups and the history of myocardial infarction can also be attributed to execution of this research. Although patients were chosen at random, a sizable portion came from cardiology wards, increasing the possibility that myocardial infarction patients would be included in this study. Additionally, there was no upper threshold of uric acid levels for the analyzed subjects therefore patients with elevated uric acid levels, which is a controversial risk factor for cardiovascular diseases, were included in this study.

Patients with a history of single episode stroke and patients without a stroke in the two stratified patient groups were tested with a Fisher exact probability test

which showed non statistically significant results. This was predicted because there is a significant overlap between the risk variables for chronic vascular dementia and single episode strokes. With the abundance of confounding variables of cardiovascular, renal, and endothelial risk factors, it could be that the potential neuroprotective effects of normal uric acid levels are diminished. While it is beyond the scope of this paper, it raises the question about whether the proposed antioxidative effects of normal blood uric acid levels have different roles in different organ systems, or if the antioxidative role of uric acid is uniquely important in neurodegeneration or general brain function.

Creatinine and serum uric acid levels on the other hand showed a moderate positive correlation and reached statistical significance. This is unsurprising as uric acid levels and creatinine, and general renal function are closely related.

There are three main limitations in this study. First, the sample size with 77 patients was relatively small. The sample size was sufficient enough to determine statistical significance in the most important test, however by having a larger study pool, the detection of all statistically significant association could have been ensured. The second drawback was that uric acid levels were a single time measurement and were not followed over a period of time, therefore any transient changes in hypo- or hyperuricemic status cannot be excluded. While patients placed on uric acid lowering medications and patients with renal insufficiency were excluded from the study, and therefore it is unlikely that overall uric acid status would change significantly, it is possible that serial measurements of uric acid levels would more confidently sort patients into appropriate hypo- and hyperuricemic categories. And lastly, while test subjects were drawn from inpatient and outpatient settings, the majority were hospitalized patients who were admitted for some medical pathology. It is therefore not possible to surely exclude any contributing factors to our results and as in many studies, dealing with hospitalized patient populations, there is a possibility that results may vary by patient population.

In conclusion, this study provides evidence that hypouricemia has potential effects on health, specifically on the rate of neurodegenerative diseases such as Alzheimer's disease. The lack of a statistically significant association for vascular dementia lends additional evidence to the potential role of uric acid as a factor in diseases mediated by specific neurodegenerative processes as opposed to a general neuroprotective effect. While no research to date has found convincing evidence for a particular lower bound of normal blood uric acid levels, this research furthers the argument that one is needed. In the absence of specific evidence-based recommendations the EULAR guidelines of maintaining blood uric acid levels between 3 mg/dL to 6 mg/dL seem prudent. Future research should focus on identifying other pathological associations with low uric acid levels and also on determining a definite lower bound of normal serum uric levels.

6. Conclusion

In conclusion, this research supports the findings of other emerging studies that there is a possible link between hypouricemia and its effect on the brain and cognitive abilities and provides further evidence for hypouricemia potentially being a risk factor for neurodegenerative diseases like Alzheimer's disease. As expected, this study did not provide evidence an association between hypouricemia and vascular dementia and hence further strengthens the potential role of uric acid as a factor in diseases

mediated by specific neurodegenerative processes as opposed to a general neuroprotective effect.

The most important finding of this study remains that there is a definite need for a lower threshold for normal serum uric acid levels, especially for patients who are receiving novel urate-lowering therapies. As of now no research has established strong support to define an optimal range for uric acid levels, however the EULAR recommendations to keep blood uric acid levels between 3 mg/dL and 6 mg/dL seem appropriate in the absence of explicit evidence-based recommendations.

Conflict of interest

The authors declare no conflict of interest.

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