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SIGNIFICANCE OF HYPOURICAEMIA IN THE DEVELOPMENT OF NEURODEGENERATIVE DISEASES

Maximiliane Trapp[1,#], Anna Mihailova[1,2], Natalija Kakurina[3], and Modra Murovska[4]

[1] Faculty of Medicine, Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[2] Orto Clinic, 1a Bukultu Str., Rīga, LV-1005, LATVIA

[3] Daugavpils Regional Hospital, 20 Vasarnīcu Str., Daugavpils, LV-5417, LATVIA

[4] Institute of Microbiology and Virology, Rīga Stradiņš University, 5 Rātsupītes Str., Rīga, LV-1067, LATVIA

[#] Corresponding author, maxitra@gmail.com

Contributed by Modra Murovska

*Hypouricaemia has received relatively little attention in the literature. As a result, there is less awareness or understanding of the potential risks of low uric acid levels. Emerging research indicates that normal uric acid levels may have an antioxidative and neuroprotective effect. This study aims to investigate possible associations between hypouricaemia and neurodegenerative disease. Data was collected from seventy-seven outpatients and inpatients who underwent routine uric acid testing, who were then stratified into patients with and without neurodegenerative disease. Patients with renal pathologies and patients using uric acid altering medications were excluded from the study. There was a significant difference in the prevalence of Alzheimer's disease between hypouricemic and normouricemic patients (*p *= 0.001), however there was no difference in the prevalence of vascular dementia (*p *= 0.45). This study provides evidence that hypouricaemia has potential effects on health, specifically on the rate of neurodegenerative diseases such as Alzheimer's disease and gives weight to the potential neuroprotective role of uric acid.*

Key words: *uric acid, Alzheimer's disease, vascular dementia.*

INTRODUCTION

Previous research on uric acid levels and pathology has focused mainly on the presence of hyperuricaemia as a risk factor for cardiovascular disease (Kuwabara, 2016). The topic of hypouricaemia has been much less studied and as a result there is little awareness or understanding of any potential risks of uric acid levels below the normal range. With the advent of safer and more effective urate-lowering medications, the potential for issues related to hypouricaemia has increased.

Recent studies (Pello *et al*., 2009; Fang *et al.,* 2013; Perez-Gomez, 2019) have found a possible association between low serum uric acid levels and the development of neurodegenerative diseases. This raises the question whether normalisation of uric acid concentration could prevent the development of neurodegenerative diseases.

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 (Maiuolo *et al*., 2016). Humans lack this enzyme, leaving uric acid as the end product. Ames *et al.* (1981) hypothesised that uric acid acts as an antioxidant by scavenging singlet oxygens and radicals and they proposed that urate is as powerful as ascorbate in its antioxidative function by reducing the oxidative stress on erythrocytes. In 2008, Sautin and Johnson published a research paper that agrees with the hypothesis of Ames *et al.* (1981) about uric acid's antioxidative function; however, they claimed that uric acid also has oxidative effects that are pro-inflammatory. They observed that uric acid in plasma acts as an antioxidant and within cells as a pro-oxidant. They called this contradiction the oxidant-antioxidant paradox (Sautin and Johnson, 2008). This paradox states that hyperuricaemia can lead to an inflammatory response causing gout, and endothelial dysfunction causing cardiovascular diseases (Kanbay *et al*., 2013), while 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 (Becker *et al*., 2019). The reduced antioxidant capacity is believed to be neurotoxic due to increased oxidative damage (Fang *et al*., 2013), but it remains unclear if this loss is sufficient to induce neurodegenerative diseases (Settle, 2014).

Mortality and serum uric acid levels. It has been shown that hyperuricaemia is an independent risk factor for hypertension, but due to many confounders it has not been found to be an independent risk factor for cardiovascular diseases as of yet (Kuwabara, 2016). Another disease that is closely related to hyperuricaemia is gout, which is managed mainly by decreasing the serum uric acid levels. The current European guidelines recommend lowering uric acid to less than 6 mg/dl, but not less than 3 mg/dl (Richette *et al*., 2016). For a long time there has been no established lower limit as little research on the consequences of hypouricaemia has been done, and it has only recently become a topic of interest. There have been several studies that investigated the mortality from high and from low uric acid levels. The EPOCH-Japan study found that low uric acid levels are associated with a higher overall mortality rate from cardiovascular diseases. They concluded that a J- or U-shaped association exists between low and high uric acid levels and cardiovascular mortality (Zhang *et al*., 2016). Another study conducted in Korea also confirmed a U-shaped, independent relationship between serum uric acid level and mortality (Cho *et al*., 2016). The relationship between mortality and hyperuricaemia can be explained by the activation of the NLRP3 inflammasome and a resulting increase of Interleukin-1ß and increased production of ROS (Braga *et al*., 2017), which then trigger arteriosclerosis (Kuwabara, 2016). Conversely, causes of mortality associated with hypouricaemia are not fully understood to date. The authors of the Korean study gave possible explanations for the observed mortality, such as malnutrition, side effects of medications that affect uric acid levels, other comorbidities, and increased risk of oxidative stress due to a reduction in the antioxidative properties of uric acid.

Causes of hypouricaemia. In the literature, hypouricaemia is defined as a serum urate concentration less than 2 mg/dl (Esparza and Garcia, 2016). It can be caused by decreased uric acid production, seen in inherited disorders such as hereditary xanthinuria or purine nucleosidase phosphorylase deficiency, or it can be secondary to urate lowering therapies that are commonly used in the management of gout. Further causes of hypouricaemia are either uric acid oxidation with derivatives of uricase, which are commonly used in oncology, and disorders that increase the urinary excretion of urate, such as inherited familial renal hypouricaemia, or acquired disorders such as Fanconi syndrome.

Inherited hypouricaemia. Cases of inherited low uric acid levels in the absence of malnutrition and other diseases that influence uric acid levels make an ideal model to investigate the possible effects of hypouricaemia. These can serve as an example of possible risks of clinical use of urate-lowering therapies without an established 'safe' lower limit for blood uric acid levels. Inherited defects that cause decreased uric acid production are very rare. The most intensively studied genetic cause for hypouricaemia is familial renal hypouricaemia, which results in increased excretion of uric acid. The prevalence for renal hypouricaemia worldwide is unknown, however cases have been reported in Japan (prevalence: 0.3%) (Nakayama *et al*., 2019) and South Korea (prevalence: 1.39%) (Son *et al*., 2016). It is caused by loss of function mutations in the renal tubular urate transporters. With a mutation in the *SLC22A12* gene (URAT1 transporter) it is referred to as renal hypouricaemia type 1, whereas with a mutation in *SLC2A9* (GLUT9) as renal hypouricaemia type 2. Most affected patients are asymptomatic, although both types have been linked to nephrolithiasis and exercise-induced acute kidney injury (EIAKI). Posterior reversible encephalopathy syndrome (PRES), a more severe disorder that presents with headache, seizures and other neurological findings, has been associated with renal hypouricaemia type 2. It was suggested that PRES is not due to severe hypouricaemia *per se*, but rather to an adverse effect of severe EIAKI (Fujinaga *et al*., 2013). More research is needed for further understanding on how renal hypouricaemia can cause posterior reversible encephalopathy syndrome. Overall, while cases of pathology related to inherited hypouricaemia are well documented, most patients affected by hypouricaemia of a genetic origin appear to be asymptomatic.

Acquired hypouricaemia. By far the most common cause of acquired hypouricaemia is due to the use of urate-lowering therapies and subsequent decreased uric acid production (Mount, 2018). In most guidelines the recommendation is to lower plasma urate below 6 mg/dl. If tophi are present, the guidelines suggest to further lower plasma urate below 5 mg/dl (Sautner *et al*., 2013; Graf *et al*., 2015; Richette *et al*., 2016; Hui *et al*., 2017; Kiltz *et al*, 2017; Yu, 2018). There are only two guidelines, the British Society for Rheumatology and EULAR recommendation (2017), mentioning potential outcomes from lower urate levels. It is believed that low urate levels increase the risk for neurodegenerative disorders (Bowman *et al*., 2010), such as Parkinson's disease, Alzheimer's disease and Amyotrophic lateral sclerosis, and that elevated levels may have a protective function (Fang *et al*., 2013; Paganoni and Schwarzschild, 2016). Furthermore, in the past decade the results of seven randomised 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) (Becker *et al*., 2005; Sundy *et al*., 2011; Saag *et al*., 2016; Bardin *et al*., 2017; Dalbeth *et al*., 2017; Tausche *et al*., 2017; White *et al*., 2018). In the largest trial, the CARES study, a statistical significant relationship between intensive urate lowering therapy and mortality was found (White *et al*., 2018). In the other trials, this relationship was not statistical significant, but mortality was highest in the arms with the greatest urate lowering effect, raising the suspicion of

safety concerns about commonly used gout medication without a lower cut-off threshold (Perez-Gomez *et al*., 2019). 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 guidelines (Richette *et al*., 2016; Hui *et al*., 2017) major published guidelines currently address the potential dangers of lowering urate levels beyond the normal range.

Adverse effects of hypouricaemia. There is still little definitive knowledge about the specific short- and long-term clinical effects of hypouricaemia. One potential danger that can occur from urate-lowering therapy with xanthine oxidase inhibitors is the accumulation of hypoxanthine and xanthine, which that could eventually cause xanthine nephropathy. This remains a theoretical concern as no cases (except for patients with tumor lysis syndrome) have been reported to date (Bellomo and Selvi, 2018). It is thought that uric acid has a protective antioxidant function and that loss of this antioxidative function can occur in cases of hypouricaemia. It is less clear if the loss of antioxidative protection due to subnormal uric acid levels is sufficient to induce neurodegenerative disease.

This aim of the study was to investigate the possible associations between hypouricemia and neurodegenerative disease.

MATERIALS AND METHODS

Study subjects. The data was collected from patients treated in Daugavpils Regional Hospital, Orto Clinic, Rīga East Clinical University Hospital, and Pauls Stradiņš Clinical University Hospital, on an outpatient or inpatient basis after consent was obtained, and consisted of a randomised cross section of patients whose serum uric acid concentration had been measured as part of their routine blood tests. These patients were not admitted for uric acid related pathology and did not display acute symptoms related to blood uric acid levels. Additionally, none of the studied patients were receiving treatment for their uric acid levels. Patients with high creatinine levels or chronic kidney diseases were excluded from data analysis due to secondarily elevated uric acid levels. Patients who did not agree to the use of their data for research purposes were also excluded from analysis. Data about patient age, height, weight and present and past medical history, with specific interest to neurodegenerative diseases, as well as laboratory data such as uric acid concentration and serum creatinine levels were also collected from the patient files. Patients with neurodegenerative diseases were diagnosed by certified psychiatrists according to the current guidelines prior to the start of this study. For the analysis, patients were then stratified into patients with neurodegenerative disease and patients without neurodegenerative disease.

Variables. In this study, hypouricaemia was defined as less than 200 μmol/l and only one measurement was taken. Creatinine levels higher than 110 μmol/l were excluded from the study. 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 the ICD-10 classification.

Statistical analysis. Statistical analyses were performed using SPSS Statistics software (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 $\alpha = 0.05$.

RESULTS

Study subjects' characteristics. Of the 100 interviewed patients, 18 were excluded due to high creatinine levels and five patients refused to be included in the research. As a result, 77 patients were included in the study. The group of patients with neurodegenerative disease included 45 patients and the mean age the group of patients without a neurodegenerative disease was 32 patients. The demographic statistics of the study population are given in Table 1.

Uric acid correlation with age and kidney function. Uric acid is excreted from the body by the kidney, the function of which decreases with age (Weinstein and Anderson, 2010). Therefore, the correlation between serum uric acid concentration and GFR was calculated. As expected, there was a moderate positive correlation ($r = 0.58$) for patients for neurodegenerative disease and for patients without neurodegenerative diseases ($r = 0.51$). Both results were statistically significant at $p < 0.05$. Additionally, the correlation between serum uric acid concentration and patient age

Table 1. Demographics of the study population

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 ± 11.0	80.3 ± 14.0
Height in cm	170 ± 7	167 ± 9
BMI	26.3 ± 11.0	28.8 ± 13.0
Uric acid in μmol/l	387 ± 210	409 ± 156
Creatinine in μmol/l	83 ± 26	76 ± 20
GFR in ml/min/1.73 m²	98 ± 16	96 ± 14
Alzheimer's disease patients	4	NA
Vascular dementia patients	40	NA
Dementia in other diseases classified elsewhere	1	NA

was tested by Pearson correlation coefficient. The results showed that in both groups there was no correlation (r = 0.0615) for patients with neurodegenerative diseases and modest correlation (r = –0.70) for patients without neurodegenerative disease and the latter one lacked statistical significance at $p < 0.05$.

Uric acid level and its association with neurodegenerative diseases in stratified age groups. The groups of patients with a neurodegenerative disease and without neurodegenerative disease were stratified into age groups of 50–79 years and 80 years to test the effect of age on vascular dementia. The mean uric acid levels for the different age groups are shown in Figure 1. The stratified groups were tested with a Fisher exact probability test to determine significance of relationships between the two age groups and the diagnosis of vascular dementia at a significance level $p < 0.05$. The stratified groups did not show statistically significant relationships between age groups and Alzheimer's disease.

Hypouricaemia and its association with neurodegenerative diseases. As a final step the patients with hypouricemic levels were compared to patients with normal uric acid levels for frequency of occurrence of vascular dementia and Alzheimer's disease. This was done with a chi-squared test of independence with a significance level $p < 0.05$. The result for a non-random association between the rate of vascular dementia in patients with hypouricaemia and patients with normal serum uric acid levels was not significant χ^2 (1, n = 77) = 0.56, $p = 0.45$, indicating no significant difference in the frequency of occurrence of vascular dementia depending on uric acid levels. However, for patients with Alzheimer's disease, the chi-square analysis for the rate of Alzheimer's disease in patients with hypouricaemia and patients with normal blood uric acid levels showed a non-random distribution. This indicates a statistically significant difference in the rate of this disease among hypo- and normouricemic patients, significant at χ^2 (1, n = 77) = 10.5, $p = 0.001$.

DISCUSSION

In this study, the possible relationship between serum uric acid and neurodegenerative diseases was explored, to provide addition information on the suggested link between low uric acid levels and loss of reduction in antioxidant capacity leading to the increased occurrence of neurodegenerative diseases.

The reasoning behind this suspected relationship is the complex role of uric acid 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 (Sautin and Johnson, 2008). 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. Multiple studies have linked these processes to neurodegenerative diseases such as Parkinson's disease, multiple sclerosis and Alzheimer's disease. However, this relationship was not shown for vascular dementia (Squadrito *et al*, 2000; Mattson, 2003; Singh, 2019). This does not come as a surprise if one takes the pathogenesis and risk factors for these diseases into account.

Alzheimer's disease is characterised primarily by the accumulation of neurotoxic metabolic products and abnormal proteins such a beta amyloid and neurofibrillary tangles (Longo and Massa, 2004; Kocahan and Doğan, 2017). This creates an environment hostile to normal brain cell function

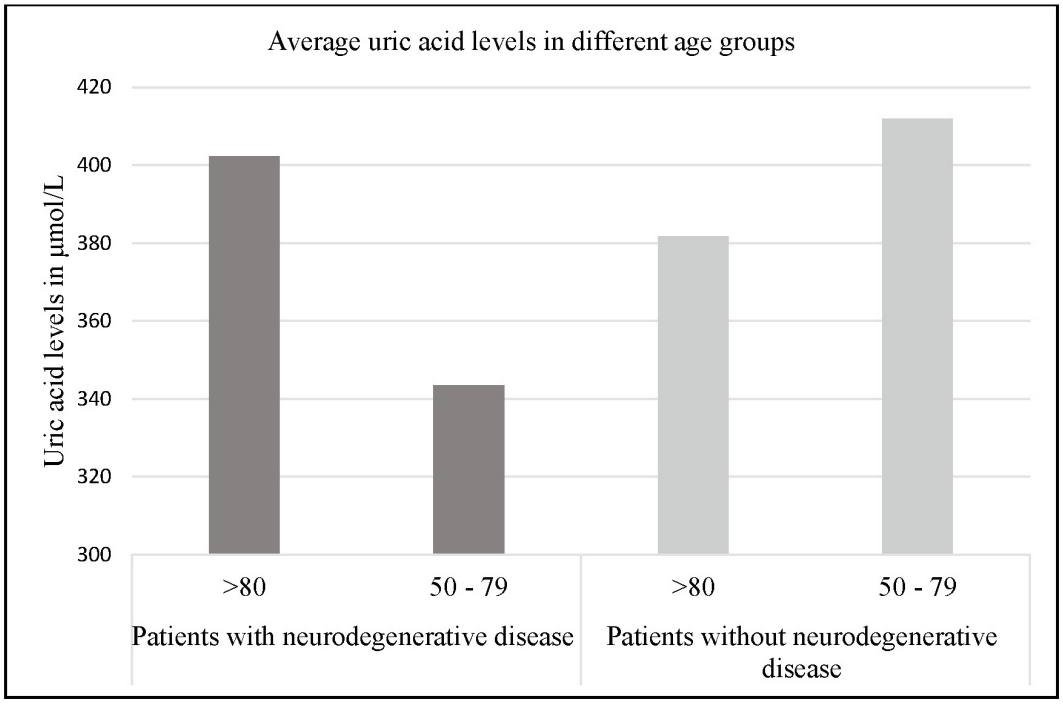

Fig. 1. Average uric acid levels after stratification of patients into age groups

and results in progressive dysregulation and synaptic dysfunction. Several studies have implicated neuronal excitotoxicity from overstimulation of N-methyl-D-aspartate (NMDA) receptors (Olivares *et al*., 2012). 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.

On the other hand, vascular dementia has shown a contradictory result in recent studies and does not seem to be associated with lower uric acid levels. This makes sense in light of the abundance of risk factors and multiple etiologies of vascular dementia. While individual neuroprotective factors may certainly play a role in the onset or extent of vascular dementia, the relative weight of such neuroprotective factors may be outweighed by the larger contributions of cardiovascular, renal, and general endothelial risk factors. With this in mind, the relationships between age and Alzheimer's disease and age and vascular dementia were explored. As expected, there was no such statistical significant relationship for Alzheimer's disease. However, the relationship between age and vascular dementia was statistical significant, indicating higher prevalence of vascular dementia with increased age.

The results of our study are further in line with other studies. The mean serum uric acid levels were compared between patients with and without neurodegenerative disease. A meta-analysis on effects of low uric acid levels found no significant difference in serum uric acid levels between patients suffering from Alzheimer's' disease and healthy individuals, but there was a trend towards lower uric acid levels among patients with Alzheimer's disease (Chen *et al*. 2014). This trend was also confirmed in our study, with no significant difference between the two groups, but lower values were noted in the group with neurodegenerative diseases. This led us to further analyse the group of patients with neurodegenerative diseases. Patients with hypouricemic levels were compared to patients with normal uric acid levels for the occurrence of vascular dementia and Alzheimer's disease. In other studies (Squadrito *et al*, 2000; Mattson, 2003; Singh, 2019), we found a statistical significant relationship between hypouricaemia and Alzheimer's disease, but not for vascular dementia.

These findings are especially important, as through the advent of safer and more effective urate lowering medications, the risk of a patient becoming hypouricemic increases. There are only two guidelines, the British Society for Rheumatology and EULAR recommendation (2017), that mention potential outcomes from lowering urate levels, and only the EULAR recommendation has defined a lower threshold plasma urate level with a recommended range between 3 mg/dl to 6 mg/dl. This range seems appropriate taking into account that we defined hypouricaemia as serum uric acid levels below 200 μmol/l (3.36 mg/dl). With more research on the link between hypouricaemia and neurodegenerative disease evolving, the range suggested by EULAR should be revisited and re-evaluate the optimal range that protects patients from losing the neuroprotection that uric acid offers.

There are three main limitations of this study. The first limitation was the sample size, which while large enough to determine statistical significance in the most important tests, could have benefited from further enlargement to ensure detection of all statistically significant associations. Secondly, serum uric acid levels were measured only once. Therefore, 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, the majority of test subjects were drawn from hospitalised patients admitted for some medical pathology. As in many studies dealing with a hospitalised patient population, there is a possibility that results may vary between the patient populations.

CONCLUSION

This study provides evidence that hypouricaemia 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.

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HIPOURIKĒMIJAS NOZĪME NEIRODEĢENERATĪVO SLIMĪBU ATTĪSTĪBĀ

Hipourikēmijai literatūrā ticis pievērsts salīdzinoši maz uzmanības. Tā rezultātā ir mazāka izpratne un zināšanas par zemā urīnskābes līmeņa iespējamo ietekmi uz veselību. Jaunākie pētījumi rāda, ka normālam urīnskābes līmenim varētu būt antioksidantīvs un neiroprotektīvs efekts. Šī pētījuma mērķis ir izpētīt iespējamās saistības starp hipourikēmiju un neirodeģeneratīvām slimībām. Dati tika savākti no septiņdesmit septiņiem ambulatorajiem un stacionārajiem pacientiem, kuriem regulāri tika veiktas urīnskābes pārbaudes. Pacienti tika sadalīti divās grupās: pacienti ar neirodeģeneratīvām slimībām un pacientiem bez neirodeģeneratīvām slimībām. Pacienti ar nieru patoloģijām vai pacienti, kuri lieto urīnskābi ietekmējošos medikamentus, tika izslēgti no pētījuma. Pacientiem ar hipourikēmiju Alcheimera slimība tika novērota ievērojami biežāk, salīdzinājumā ar tiem pacientiem, kuriem urīnskābe bija normālā līmenī (p = 0,001). Turpretī saslimšanas biežums ar vaskulāro demenci nebija atkarīgs no urīnskābes līmeņa asinīs (p = 0,45). Pētījums pierāda, ka hipourikēmijai varētu būt ietekme uz cilvēka veselības stāvokli, īpaši uz neirodeģeneratīvo slimību izcelšanās biežumu, kā piemēram Alcheimera slimību, un norāda uz urīnskābes iespējamo neiroprotektīvo lomu.