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Lesch-Nyhan Syndrome with Self-harming and Choreoathetosis after Improvement of Hyperuricemia: a case report

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Abstract

Lesch-Nyhan syndrome (LNS) is an inborn error of metabolism. Choreoathetosis, mental retardation and self-harming are the three symptoms. A genetic test that analyses the gene encoding hypoxanthine-guanine phosphoribosyltransferase (HPRT) and blood tests showing hyperuricaemia support the diagnosis. However, the relevance of these test results to clinical symptoms is unclear. A 25 years-old man consulted our hospital for self-injury and choreoathetosis. He had epilepsy and mental retardation. He was also suffering from hyperuricemia and was prescribed allopurinol. These symptoms appeared with the improvement of hyperuricemia. He was suspected to have LNS. Metabolomic analysis of his urine before and after the allopurinol loading test was performed by gas chromatography-mass spectrometry (GC/MS) using dry filter paper urine samples as samples. The results showed that he was LNS.This case suggests that LNS is a condition that causes epileptic seizures and that rapid fluctuations in uric acid levels can cause choreoathetosis and self-harming. GC/MS using dry filter paper urine samples was a simple and valid test. This report also shows that genetic diagnosis opportunities are available to patients who have difficulty attending hospitals with advanced genetic analysis systems in urban areas.

Keywords: Lesch-Nyhan syndrome; Hyperuricemia; Metabolomic analysis; Gas chromatography-mass spectrometry.

Introduction

Lesch-Nyhan syndrome (LNS) is a hereditary disease, also known as hypoxanthine guanine phosphoribosyl transferase (HPRT). Choreoathetosis, mental retardation and self-harming are

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the three symptoms of LNS [1]. In general, LNS is diagnosed during the period from infancy to 2 years of age. Lab data often shows high blood uric acid levels and high uric acid / creatine ratios [1].

Another method to assist in diagnosis is a genetic test that analyzes the gene encoding hypoxanthine-guanine phosphoribosyltransferase (HPRT), but there are not many advanced medical institutions that can perform this test. Therefore, we need more easy tests to support the diagnosis of LNS. In addition, genetic diagnosis is not a marker to predict the occurrence or severity of self-harming or choreoathetosis in LNS. Factors that control these symptoms have not yet been identified [2].

In this article we report on the association between blood tests and neurological and psychiatric symptoms in LNS. We also report on a simpler urine test that may be useful in the diagnosis of LNS when access to advanced medical facilities is difficult.

Case report

Clinical history

A 25 years-old man consulted our hospital's branch clinic for obese. He was 148 cm tall, weighs 58 kg (Body mass index:26.5). Blood tests showed that his uric acid level was high (8.8 mg/dl). He was diagnosed as hyper-uricemic, and allopurinol 100 mg was started. Diet and exercise therapy were also initiated.

Living environment

The branch clinic was set up inside a Nursing home where he lived in. The Nursing home was located in the mountains, far from our hospital. And the residents, many of whom were mentally retarded, hated to go to the hospital because to do so, they had to sit quietly on the bus seat for a long time. And the travel was also a big burden for the caregivers working in the Nursing home, because sometimes the residents who did not want to ride the bus would beat the caregivers. Therefore, I regularly drove from the hospital to the infirmary to treat them.

Medical history

Since his childhood, he had been diagnosed with mental and physical developmental disorders. Twenty years ago, he was diagnosed with severe mental retardation. Since the same time, he has had convulsive seizures with loss of consciousness.

He was also diagnosed with idiopathic generalized epilepsy. Antiepileptic drugs (carba-mazepine 600 mg, sodium valproate 600 mg) were prescribed, and his seizures disappear-red. He had no family history of neurological disorders or other diseases.

Clinical Findings

Hyperuricaemia and clinical symptoms

After a month, his uric acid level improved to 6.4 mg/dl. But he came to have symptoms of biting his fingers and lips by himself and choreoathetosis, which indicates chorea and athetosis at the same time. I considered the worsening of its symptoms to be associated with a rapid improvement in hyperuricaemia.

Therefore, allopurinol was stopped. The symptoms then gradually improved and disappeared after two months. The hyperuricaemia also improved, albeit slowly, due to diet and exercise therapy. 6 months later, his uric acid level decreased to 6.0 mg/dL and his weight decreased to 51 kg (Body mass index: 23.5).

At the nursing home owned by the hospital, where the patient lives, 2mL of each of his urine before and after allopurinol loading was collected and adsorbed onto cellulose (100%) based filter paper (size; approximately 60 x 80 mm, thickness; 0.7 mm). Each filter sample was stored at room temperature and mailed to the laboratory for analysis by GC/MS [2]. As a result, hypo-xanthine was +1.0SD, xanthine was +3.7SD, and urate was +2.3SD in the urine of just before allopurinol loading (Table 1).

Table 1. Before allopurinol loading Urine Amino acids, uracil, otic acid quantitative value.

Urine Amino acids, uracil, otic acid quantitative value			
Total Creatinine 11.09μmol/ml			
Chemical compound	Control score (Average±2SD)	Quantitative value for each Total Creatinine	Mean+n SD
Uracil	1,67E+01 1,48E-01	3,48E+00 3,08E-02	
Orotate	2,53E+01 2,24E-02	7,99E+00 7,07E-02	4,6
Alanine	2,85E+01 2,52E-01	3,91E+00 3,46E-02	
Giycine	3,61E+02 3,19E+00	1,17E+02 1,03E+00	
Valine	7,91E+00 7,00E-02	5,62E-01 4,98E-03	
Leucine	7,86E+00 6,96E-02	1,89E+00 1,67E-02	
Isoleucine	3,35E+00	1,86E-01	

	2,96E-02	1,65E-03
Methionine	4,17E+00	1,06E+00
	3,69E-02	9,37E-03
Phenylalanine	1,15E+01	3,47E+00
	1,02E+01	3,07E-02
Lysine	2,54E+02	1,55E+00
	2,25E+00	1,33E-02
Tyrosine	2,25E+01	6,89E+00
	2,25E-01	6,10E-02
Cystine	2,57E+01	8,39E+00
	2,27E-01	7,42E-02
Homocystine	0,00E+00	0,00E+00
	0,00E+00	0,00E+00

SD: Standard deviation.

In addition to that, hypoxanthine was +0.5SD, xanthine was +1.7SD, and urate was +0.8SD in the urine of 27 hours after allopurinol loading (Table 2). His head non-contrast computed tomography (CT) and electrocardiogram (ECG) and Electroencephalography (EEG) showed no abnormal findings.

The patient was diagnosed with LNS. The patient was to continue an exercise and diet treatment for obesity and hyperuricaemia. Later, self-injury and choreoathetosis did not recur in that patient. The patient is living well.

Table 2. After 27 hours of allopurinol loading Urine Amino acids, uracil, otic acid quantitative value.

Urine Amino acids, uracil, otic acid quantitative value			
Total Creatinine 11.03μmol/ml			
chemical compound	Control (Average± 2 SD)	Quantitative value per total creatinine	Mean+n SD
Uracil	1,67E+01	4,25E+00	
	1,48E-01	3,76E-02	
Orotate	2,53E+00	5,16E+00	3,7
	2,24E-02	4,57E+00	
Alanine	2,85E+01	4,73E+00	
	2,52E-01	4,19E-02	
Giycine	3,61E+02	1,23E+02	
	3,19E+00	1,09E+00	
Valine	7,91E+00	5,95E-01	
	7,00E-02	5,27E-03	

Leucine	7,86E+00	2,19E+00
	6,96E-02	1,94E-02
Isoleucine	3,35E+00	2,05E-01
	2,96E-02	1,82E-03
Methionine	4,17E+00	9,05E-01
	3,69E-02	8,01E-03
Phenylalanine	1,15E+01	3,57E+00
	1,02E+01	3,16E-02
Lysine	2,54E+02	3,87E+00
	2,25E+00	3,43E-02
Tyrosine	2,25E+01	5,91E+00
	2,25E-01	5,23E-02
Cystine	2,57E+01	6,11E+00
	2,27E-01	5,40E-02
Homocystine	0,00E+00	0,00E+00
	0,00E+00	0,00E+00

SD: Standard deviation.

Discussion and Conclusion

In the classification of epilepsies, about 70% of them are idiopathic epilepsies with no known cause. In other words, symptomatic epilepsy with a known causative disease accounts for only about 30% of all epilepsies. In some cases of idiopathic epilepsy, the diagnosis is latent because no characteristic clinical or laboratory findings were available at the time of diagnosis, and the diagnosis is later changed to symptomatic epilepsy when the causative disease is identified [3].

In this case, the patient was also diagnosed as having idiopathic generalized epilepsy, but the true nature of the epilepsy may be symptomatic epilepsy associated with LNS. In the treatment of hyperuricemia, rapid lowering of uric acid levels with high-dose allopurinol exacerbates gout attacks [4].

Likewise, we conclude that allopurinol rapidly lowering uric acid levels was the cause of choreoathetosis and self-harming.LNS has a similar group of diseases; HPRT partial deficiency (Lesch-Nyhan variants) is one of that group, with hyperuricemia and severe motor and cognitive impairment but without self-injury. Recent studies have shown that partial HPRT deficiency has two subgroups: one is HPRT-related neurological dysfanction (HRND) with neurological and behavioral abnor-malities but without self-injury.

The other is HPRT-related hyperrunicaemia (HRH), which has hyperuricemia but no neurological or

behavioral abnormalities. However, as in this case, no group has been reported in which improvement of hyperuricemia leads to the appearance of neurological and behavioral abnormalities [5].

There may be a subgroup of LNS in which fluctuating uric acid levels lead to the emergence of self-injurious behavior and choreoathetosis. The light footwork of gas chromatography-mass spectrometry (GC/MS) using dry-filtered urine samples is superior to genetic testing.

Although the test does not yet have a cutoff value for definitive diagnosis, both high scores are indicative of LNS [2]. The main advantage of using paper-absorbed urine specimens as opposed to blood specimens is that they do not have to be transported in a frozen state. This method provides an opportunity for people who would not otherwise have access to testing, such as the residents of the nursing home without a freezer mentioned in this report.

This study will be useful not only for the rural areas of Japan, but also for people living in areas with poor access to healthcare in the world. In the future, it is hoped that cutoff values for diagnosis can be determined in this simple and inexpensive test.

LNS has a subtype in which behavioral abnormalities appear due to fluctuations in uric acid levels, and GC/MS is useful for its genetic screening.

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Conflict of interest: T. T. Ishida was the patient's primary care physician and contributed to the literature review and manuscript preparation. T. Ishida reviewed the literature and contributed to the preparation of the manuscript.

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