증 례

Lesch-Nyhan 증후군 장기 추적관찰: 분홍 기저귀

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A Long Term Follow Up Two Cases of Lesch-Nyhan Syndrome Pink Diaper

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Lesch-Nyhan syndrome (LNS) is an Clinical symptoms can range from mild to severe depending on residual enzyme activity and genetic mutations. In Korea, 27 cases of LNS have been reported. We report the results of an 11-year comparative follow-up of two cases of children who visited because of pink diapers, one who died from LNS with no residual enzymes and one case with partial residual enzymes. Case 1: During follow-up, seizures, developmental delay, and regression were observed. The boy experienced insomnia and severe constipation. He exhibited self-mutilating behavior, a grand mal seizure, scoliosis with severe spasticity, truncal hypotonia, choreoathetoid movement, and ataxia. After prolonged emaciation, staghorn calculi, and recurrent pneumonia, the patient died suddenly at the age of 11 years. Genetic testing revealed a hemizygous HPRT1 variant (c.151C>T (p.Arg51Ter)). Uric acid level was 10.5 mg/dL (normal range: ~3.5-7.9) and HPRT activity 0.02 nmol/hr/spot (10-23.8 nmol/hr/spot). Case 2: During follow-up, the patient remained underweight. He has normal intelligence attending primary school. Self-mutilation symptoms were not observed. Regular renal ultrasonography did not reveal urolithiasis. The patient had a hemizygous HPRT1 variant (c.35A>C (p.Asp12Ala)). Uric acid level and HPRT activity were 11 mg/dL and 0.56 nmol/hr/spot. Pink diapers after the neonatal period and severe protein aversion, neurological problems, and kidney stones, differentiation for LNS is necessary. When suspected, serum uric acid levels, HPRT enzyme activity, and molecular biological tests may be helpful in predicting the prognosis of LNS.

Key words: Lesch-Nyhan syndrome, Uric acid, HPRT, Self-mutilation, Nephrolithiasis, Gout, Allopurinol

Introduction

Lesch-Nyhan syndrome (LNS) is an X-linked recessive disorder caused by a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme; an enzyme responsible for recycling purines[1)].

Purines are nitrogen-containing compounds found in many foods, including organ meat, poultry, and legumes. In the absence of HPRT, the purines hypoxanthine and guanine are not incorporated into the

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nucleotides. This leads to hyperuricemia and the accumulation of sodium urate crystals in the joints and kidneys[2].

In Korea, 26 LNS cases have been reported[3-19] (Table 1). Here, we report long-term (11 years in case 1 and 14 years in case 2) follow-up of two Korean LNS cases, determined by the presence of pink-colored diapers. The aim of this study was to assess the evolution of LNS and possible long-term complications in LNS-affected patients.

Table 1. Reported Korean Lesch-Nyhan Syndrome

Case (diagnosis department)	Age at diagnosis	C.C	Family History	Laboratory finding	Molecular finding	Ref
Case.1 (Pediatric)	8m	Orange colored urinary stone	No information	No information	HPRT1 p.D80G mother normal	3
Case.2 (Dental)	7y	Self mutilation dental hygine	No information	No information		4
Case.3 (Dental)	12	History of Lesch NyhanSyndrome, teeth grinding, developmental delay, involuntary movement disorder	No information	No information	No information	4
Case.4 (Dental)	2y1m	Self mutilation especially oral area, involuntary motor problem	Family history+ maternal cousins	No information	No information	5
Case.5 (Pediatric) (Dental)	1y7m	Poor oral intake, dehydration and irritability, urine uric acid crystal, Acute renal insufficiency, metabolic acidosis, gross motor delay, developmental delay, infantile spasm, increased DTR of lower extremities	No information	Serum uric acid: 15.2mg/dL urine uric acid/cr ratio 4.6 uric acid excretion: 155 mg/kg/day (ref. 17.8 mg/kg/day)	HPRT 649delA, mother normal	6
Case.6 Case.7 family (younger brother) (Rehabilitation)	5y	3years Self mutilation, oral ulcer, finger injury, quadriplegia, developmental delay	Brother has Lesch-Nyhan	Uric acid: 11.2 mg/dl urine uric acid: 46 mg/dl	c.124_126del p.142del	7
Case.7 (elder brother) (Rehabilitation)	11y	MR, Self mutilation, Cerebral Palsy	No information	Uric acid: 14.1 mg/dl	c.124_126del p.142del	7
Case.8 (Rehabilitation)	12y	Intussusception, MR, urine uric acid crystal, 2 years self mutilation, involuntary motor problem, aspration pneumonia, Renal stone Tx 4 times, swallowing problem, Died by asphyxia	No information	Uric acid: 15.5 mg/dl urine uric acid: 11.9 mg/dl Renal failure, staghorn calculi HGTRT: 0	No information	7
Case.9 (Dental) (Psychiatric)	4y	Self mutilation, teeth extraction, aggressive behavior, easy frustration, sertraline 12.5 mg, risperidone 0.25 mg	Elder brother had Lesch-Nyhan	No information	No information	8
Case.10 (Dental)	13y 9m	Self mutilation, teeth extraction, with mouth guard	Younger brother had Lesch-Nyhan	No information	No information	9
Case.11 (anesthesiology)	18y	developmental delay, choreoathetosis, mental retardation, spasticity, compulsive self-mutilation, renal staghorn calculi followed by obstructive nephropathy, and arthritis	No information	Low HGPRT, BUN 13 mg/dl, Cr 0.7 mg/dl, Hb 12.9 g/dl, Ht 39%, Uric acid(Allopurinol after treatment) 3.1 mg/dl (ref. 3-7 mg/dl)	No information	10
Case.12 (anesthesiology)	5y	Renal stone, developmental delay, Self mutilation, UTI, Extracorporeal shock wave lithotripsy	No information	Low HGPRT, Mutation, uric acid 2.14 mg/dl, BUN 13.23 mg/dl, Cr 0.49 mg/dl, K 4.5 mEq/L	No information	11
Case.13 (Internal medicine)	14y	Multiple tophi with arthritis,	Maternal uncle with gouti arthritis	Uric acid 23 mg/dl, Cr 18.19 mg/dl, HGPRT 0	No information	12

Table 1. Continues

Case (diagnosis department)	Age at diagnosis	C.C	Family History	Laboratory finding	Molecular finding	Ref
Case.14 (Dental)	2y	Self mutilation, mouth guard	No information	No information	No information	13
Case.15 (Dental)	2y	Self mutilation, teeth extraction	No information	No information		13
Case.16 (Pediatric)	7y	Gross hematuria, recurrent abdominal pain	No information	Uric acid 13.6 -> 2.6 mg/dl, urine RBC 3+,uric acid crystal in urine, HPRT 0.04(ref 5.29-14.87), APRT 6.28 (ref. 1.32-3.22), CT Lt hydronephrosis and ureter stone.	No information	14
Case.17 (Pediatric)	No information	No information	No information	Undetectable, HPRT enzyme	310insG	15
Case.18 (Pediatric)	No information	No information	No information	Undetectable, HPRT enzyme	310insG	15
Case.19 (Pediatric)	No information	No information	No information	Undetectable, HPRT enzyme	533-9T->A	15
Case.20 (Pediatric)	No information	No information	No information	Undetectable, HPRT enzyme	Q109X	15
Case.21 (Pediatric)	No information	No information	No information	HPRT 0.011 nmol/min/mg hemoglobin	289delGT	15
Case.22 (Pediatric)	No information	No information	No information	Undetectable, HPRT enzyme	631delA	15
Case.23 (Dental)		Self mutilation, teeth extraction, mouth guard	No information	No information	No information	16
Case.24 (Dental)	10y	Self mutilation, acrylic splint, removable lip bumper	No information	No information	No information	17
Case.25 (Pediatric)	7m	Lesch-Nyhan	No information	No information	No information	18
Case.26 (Rehabilitation)	6m	No information	No information	No information	No information	19

Participants and methods

1. Participants

This study included two cases, both of which were determined by the presence of pink diapers. The LNS diagnosis was based on clinical features, high uric acid levels, decreased HPRT enzyme activity, and molecular analysis of the HPRT1 gene[20].

Methods

Measurement of HPRT enzyme activity was assayed in hemolysates using a radiochemical technique[20] (Case 1) or dried blood spots on filter paper[21] (Case 2).

HPRT exon (1-9) variations were determined. Patient genomic DNA was PCR amplified, with the nine HPRT exon-specific primers. Next, the PCR products were directly sequenced using an ABI3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Both patients were examined, using clinical and laboratory assessments, for 11years in case1 and 14 years in case 2.

Case History

1. Case 1

Case 1 was of a male born to non-consanguineous parents by induced vaginal delivery, following a pre-

mature membrane rupture, at 40 weeks with a normal birth weight (2,820 g) and no family history of neurological disorders (Fig. 1). The patient failed to thrive, exhibited severe protein aversion, and presented with pink diaper staining. At two months old, seizures occurred with weak crying, and the patient developed spasticity and choreoathetoid movement. Developmental delay was evident, followed by acute regression. Poor oral feeding and a strong aversion to dairy products (refusal to consume formula) was observed. Owing to developmental delay, at 11 months of age, the patient visited a rehabilitation clinic. Growth parameters were as follows: weight, 8 kg (25-50th percentile); height, 74 cm (10-25th percentile); and head circumference, 46 cm (50-75th percentile). The patient was able to roll over; however, he exhibited head lag. Although his sucking ability was weak, bottle feeding was possible. Developmental evaluation was performed using the Bayley test(Korean Bayley Scales of Infant and Toddler Development-II (K-BSID-II)). It revealed a neuropsychiatric motor development score equivalent to that of 3 to 4 months old normal child. The patient was able to make eye contact, hold toys, smile, and cry. Gross motor function results were in the 13th percentile. The patient had increased muscle tone and hyperactive Deep Tendon Reflex (DTR). The rehabilitation clinic diagnosed his condition as spastic diplegic cerebral palsy. Electroencephalography (EEG) revealed seizures. Brain magnetic resonance imaging Magnetic Resonance Imaging (MRI) showed diffuse cerebral atrophy. Hearing and visual evaluation results were within normal limits. The patient was treated for recurrent urinary tract and respiratory infections. The patient continued to participate in rehabilitation treatment programs. At one year of age, he showed a grade 2 head lag; however, he could hold his head at a 45° angle. At 2 years six months of age, the patient had insomnia symptoms, severe constipation, and self-mutilating behavior (lip-biting) was observed. The muscle relaxants, valium and baclofen, were used to treat spasticity and postural problems. One month later, he was diagnosed with autosomal recessive childhood type muscular dystrophy, resembling that of Duchenne or Becker muscular dystrophy. Although he was unable to control his head, he played with toys and moved by rolling over. At 2 years nine months of age, the patient exhibited intermittent upward gaze and functional intestinal disorders that presented as paralytic ileus or constipation. After teething, recurrent stomatitis was observed and required ENT clinic visits; this was later recognized as a self-mutilating behavior. At three years of age, seizures, developmental delay, and developmental regression were evident. Truncal hypotonia at rest and involuntary movements were observed when extensor tone was increased. At 3 years six months of age, spasticity and rigidity were observed at the rehabilitation clinic. A medication for spasticity was introduced. The patient presented with a fever and upper respiratory tract infection. At this time, pink diapers and elevated blood uric acid levels were observed. At three years and seven months of age, neurological symptoms, including intermittent upward gaze and swallowing difficulties were observed. At three years and eight months, the patient maintained a four-legged crawling position, to support his weight. In addition, fluctuating spasticity, generalized respiration, and swallowing difficulties were observed. Abdominal radiography revealed severe constipation with a paralytic ileus. Despite intermittent hand muscle

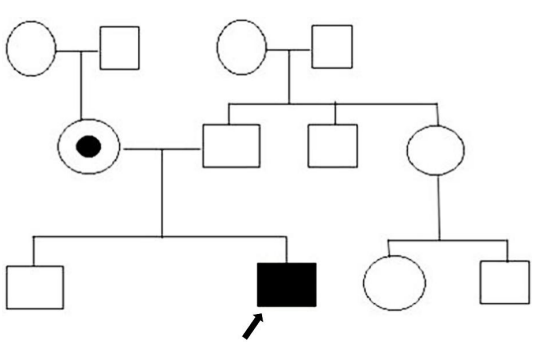

Fig. 1. Case 1 family pedigree.

spasms, hand manipulation and coordination were maintained. At four years of age, experienced a generalized tonic-clonic seizure and he was diagnosed symptomatic epilepsy. From four years and seven months of age, overactive disorder, mental retardation, and stereotyped movements were observed. At four years 10 months of age, scoliosis of the right thoracic spine was noted. At five years and seven months of age, he was able to control his head for short periods; however, emotional instability was detected. The baclofen and seizure medication dosage was increased. At five years and nine months, insomnia, muscle rigidity associated with scissoring legs, spasticity, and truncal hypotonia progressively worsened. At six years of age, he was diagnosed with Lesch-Nyhan syndrome; the diagnosis was based on high uric acid levels and low HPRT enzyme activity. Thereafter, allopurinol was used to lower the uric acid levels. Spasticity of extremities, truncal hypotonia, choleoathetoid movement, and ataxia continued to worsen until six years and 6 months. At six years and 10 months of age, he was able to roll over and crawl, and exhibited staggering movement with a wide-based gait. At seven years of age, self-mutilation, especially tongue bites, was more aggressive. However, oral-motor coordination was maintained. His emotional state was labile, and easily frustrated. The patient experienced severe constipation; bowel movements were stimulated with laxatives or enemas. At seven years and six months of age, the severity of conditions such as self-mutilation, constipation, athetoid movement, ataxia, and pink urine increased. Allopurinol relieved pink urine staining; however, protein aversion and cachexia were observed. At nine years and nine months of age, scoliosis with severe spasticity of the extremities and acute life-threatening episodes with irregular breathing began. At 10 years of age, severe emaciation, nephrolithiasis with staghorn calculi, and recurrent pneumonia were observed. Growth parameters revealed that the patient height was between the 20th and 50th percentile while his weight was lower than that of the 5th percentile. The patient lost ambulation, head control, hand manipulation skills and scissoring both legs. The patient died suddenly at the age of 11 years (Fig. 2).

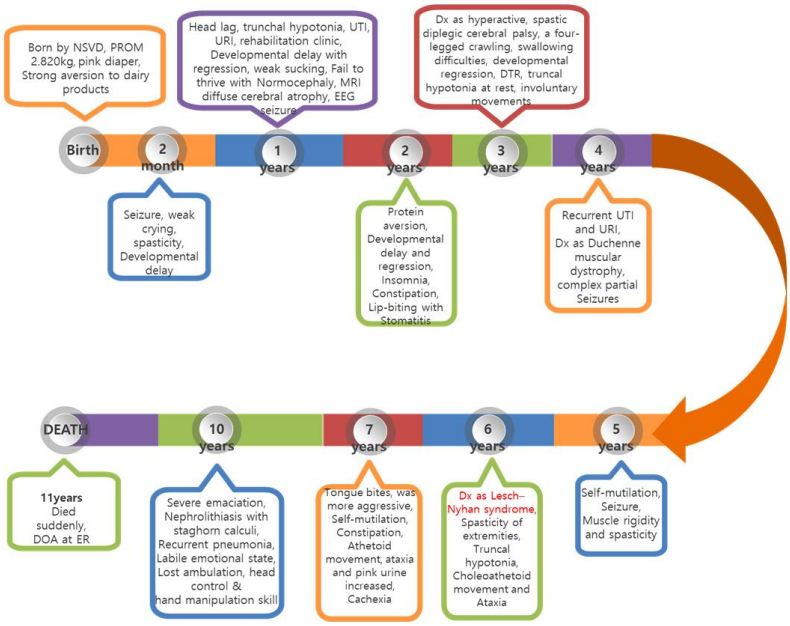

Fig. 2. Time line of case 1.

2. Case 2

A 4-year-old male patient presented with persistent pink urine and pink diaper staining. His mother experienced severe morning sickness during pregnancy. The patient was born via cesarean section at 40 weeks of gestation with normal birth weight (2,700 g). The patient was initially breastfed and switched to formula at one month of age. Poor feeding was observed after the introduction of formula. Concurrently, he exhibited a poor appetite and picky eating habits. Past medical history included hospitalization for enteritis at 3-4 months. He began walking at one year of age. The patient's language development was normal, and at 18 months of age, he was able to talk to his parents. At two and four years of age, development was normal. He had a 3-year younger sister and male cousins (from a maternal uncle) who were normal (Fig. 3).

At four years of age, he visited a genetic clinic and was extremely sensitive and nervous. In addition, poor appetite was observed. Serum uric acid levels were evaluated using pink diapers. The uric acid level increased to 11 mg/dL. As LNS was suspected, HPRT activity was measured in erythrocytes. Decreased enzyme activity (0.56 nmol/hr/spot; ref: 10-23.8 nmol/hr/spot) was observed. Urine organic acid analysis revealed the presence of uracil, purine metabolites, and dicarboxylic aciduria. Allopurinol treatment was initiated immediately.

During follow-up for 14 years, the patient was underweight. He was in fifth grade, and his academic performance at school was satisfactory. The patient's brain function and development were normal. There was no self-utilization. Regular renal ultrasonography revealed no urolithiasis.

Results

HPRT enzyme activity was significantly lower in Case 1 0.02 (10-23.8 nmol/hr/spot) than in Case 2 0.56 (10-23.8 nmol/hr/spot) (Table 2). Molecular evaluation of HPRT1 revealed a c.151C>T(p.Arg51X) mutation in Case 1 (Fig. 4) and a c.35A>C p.Asp12Ala mutation in Case 2 (Fig. 5).

The initial serum uric acid levels were 10.5 and ~4.4-11 mg/dL (ref. 3.5-7.9) in Cases 1 and 2, respectively. Pink-colored diapers were more prevalent and pronounced in Case 1 than in Case 2 (Fig. 6).

A brain MRI in Case 1 showed cerebral atrophy at the following ages: at 11 months and at two years and seven months (Fig. 7). In this patient, the EEG results were normal (Fig. 8). At four years and six months, seizure activity was observed.

Ultrasonography showed hydronephrosis and kidney stones, which had progressed to staghorn calculi in Case 1 (Fig. 9). Regular renal sonography revealed no urolithiasis in Case 2 (Fig. 10, 11).

Case 1 had been diagnosed as cerebral palsy until exhibited six years of age, when confirmed Lesch-Nyhan disease. The most important clinical clue was pink colored diaper.

Case 2 showed pink diaper and poor oral intake with protein aversion. He has been diagnosed as Lesch-Nyhan disease at age of 6 month of age.

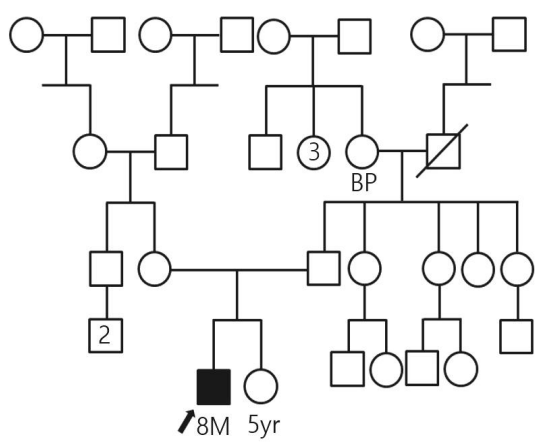

Fig. 3. Case 2 family pedigree.

Table. 2 Laboratory Evaluation in two cases

	Case 1 (6 years of age)	Case 2 (6 months of age)	Ref.
Uric acid (mg/dL)	10.5	11 4.4–10.4 (2011) 6.5 (2019) 6.1 (2020)	3.5–7.9
APRT	7.5 (0.5–7 nmol/hr/spot)	3.33 (0.5–7 nmol/hr/spot)	
HPRT	0.02 (10–23.8 nmol/hr/spot)	0.56 (10–23.8 nmol/hr/spot)	
Neopterin (mmol/mol Creatinine)	0.9	0.25 (2010) 0.31 (2011)	0.2–1.7
Biopterin (mmol/mol Creatinine)	0.2	0.81 (2010) 0.97 (2011)	0.5–2.7

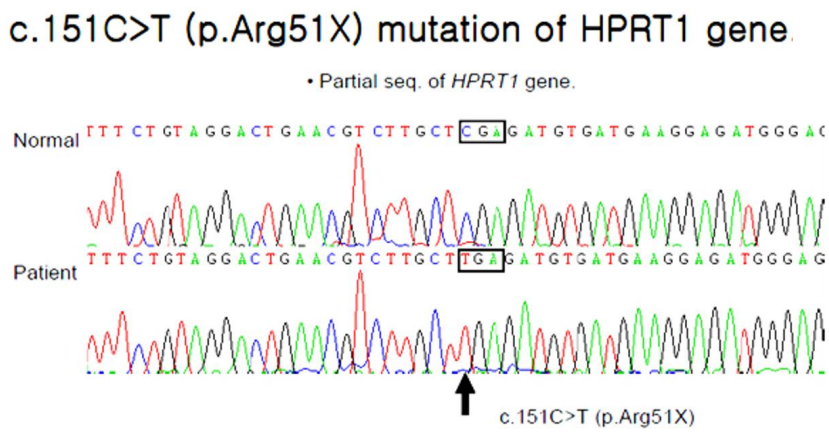

Fig. 4. Molecular results case 1.

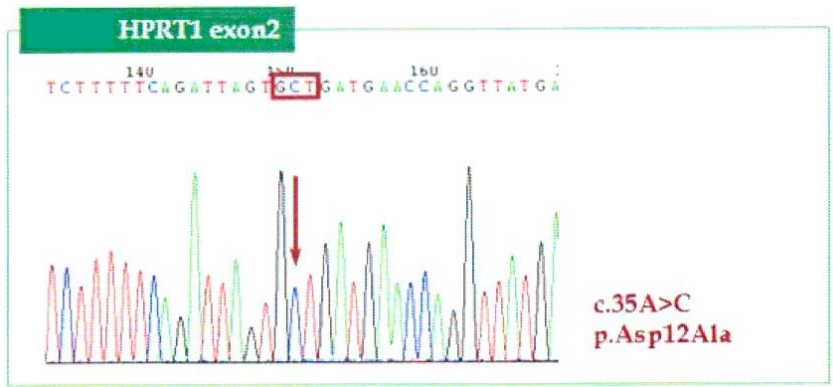

Fig. 5. Molecular Results Case 2.

Discussion

In Korea, 26 LNS cases have been reported[3–19]. The majority of cases were established LNS diagnosis by self-mutilation and developmental delays. Two cases were discovered due to renal stones[10,14] while one case was discovered due to arthropathy[12] and pink/orange-colored urine[3]. Nine cases were reported by dentists,

Fig. 6. Pink colored diaper.

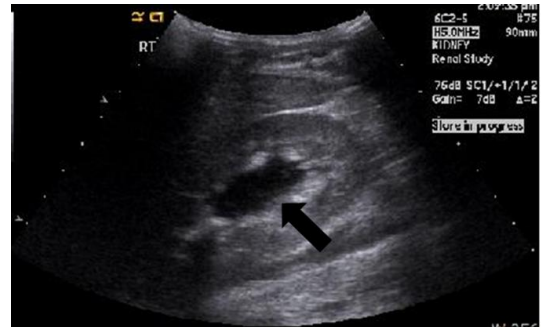

Fig. 9. Case 1 hydronephrosis.

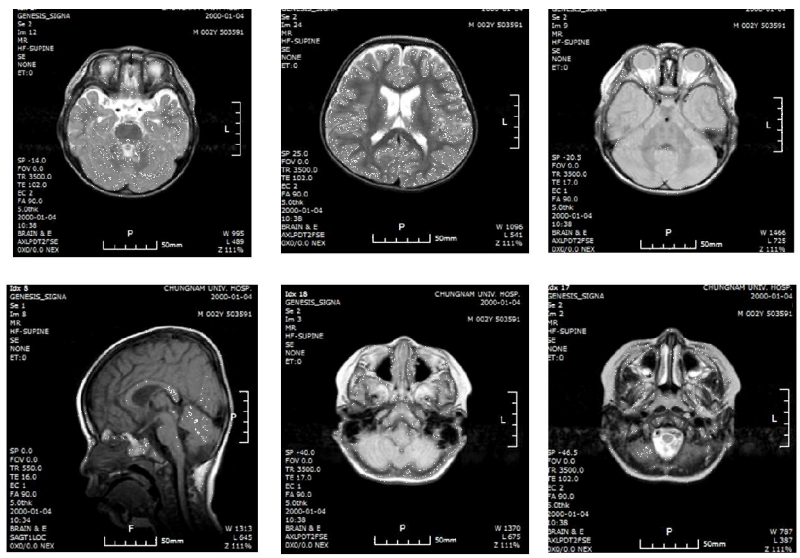

Fig. 7. Brain MRI T2 weighted axial view case 1 showed diffuse cerebral cortical atrophy in both fronto-temporal lobe.

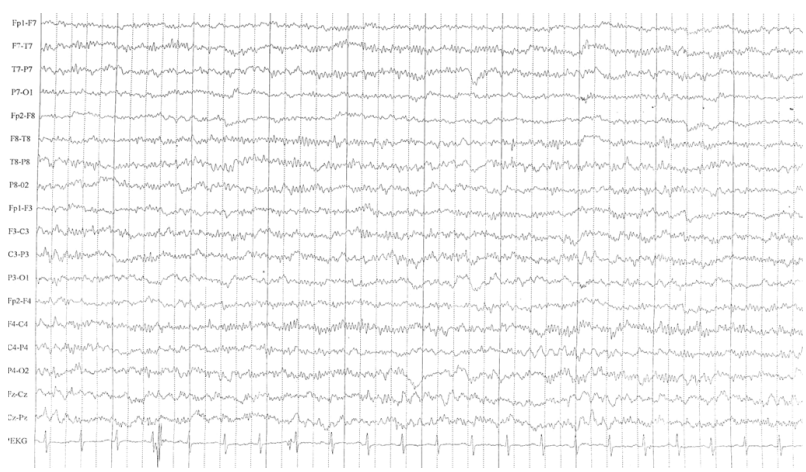

Fig. 8. Case 1 EEG. The background activity of the EEG is a low-voltage beta wave, but it is presumed to be a slow wave with sporadic spikes.

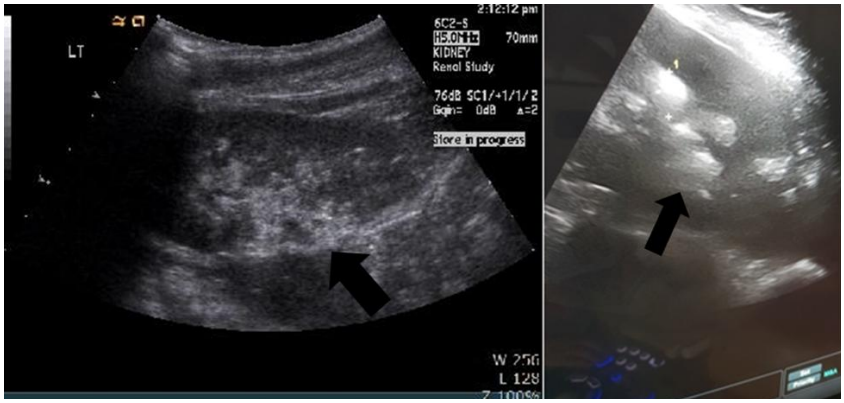

Fig. 10. Case 1 multiple renal calcification/kidney stones.

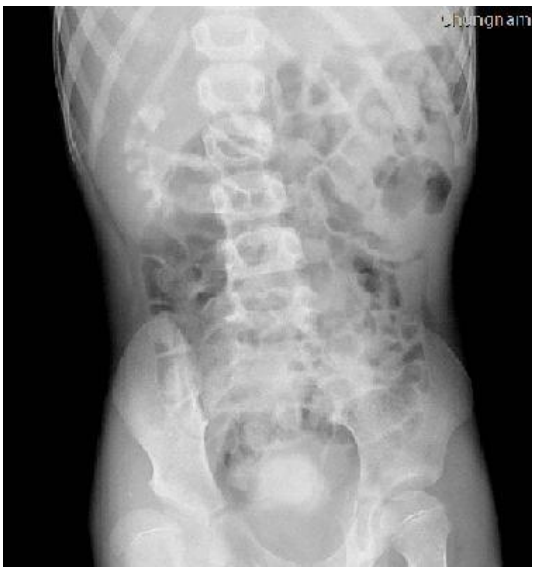

Fig. 11. Case 1 staghorn calculi.

10 by pediatricians, two by anesthesiologists and pain medicine, four by rehabilitation and one case by internal medicine physician.

Our literature review of LNS in Korea revealed that the life expectancy of patients with LNS, with active medical treatment, was between 20 and 30 years. In the absence of treatment, renal failure can occur within 10 years[22]. Renal failure and aspiration pneumonia were significantly associated with LNS induced death; however, in some LNS patients, death occurred suddenly with an unexplained or unknown cause[22,23].

Molecular evaluation of LNS in Korean patients (23 independent pedigree patients) revealed the presence of 20 different HPRT1 mutations, including six novel mutations. The most common mutations were truncating mutations, including nonsense and frameshift mutations (45%). Large deletions in HPRT1 were identified in exons 1–9, and chr X:134,459,540–134,467,241 (7702 bp), including the 5′–untranslated region, exon 1, and a portion of intron 1[24].

In Case 1, the c.151C>T(p.Arg51X) mutation (Fig. 4) resulted in severe phenotype and low enzyme activity. In contrast, Case 2 with the c. 35A > C p. Asp12Ala mutation had a mild phenotype, more residual enzyme activity, and did not exhibit self–mutilation behavior.

Conclusion

Although normal serum uric acid levels were maintained through allopurinol treatment in Case 1, life–long feeding problems, chronic gut motility dysfunction, sleeping difficulties, progressive neurologic deterioration, and nephrolithiasis were observed. In addition, pink diapers are a clinical sign of LNS that can be used as a tool for early LNS diagnosis. Overall, pink diapers, serum uric acid levels, HPRT enzyme activity, and molecular data are prognostic markers of LNS.

요 약

Lesch-Nyhan syndrome (LNS)은 X-염색체 열성 장애로 퓨린 재활용 효소인 hypoxanthine-guanine phosphoribosyltransferase (HPRT)의 결핍으로 인해 발생하는 선천성 대사질환이다. 임상 증상은 잔여 효소 활성도 및 유전적 돌연변이에 따라 다양하다. 국내에서는 27례의 LNS 사례가 보고되어 있다. 분홍색 기저귀로 방문했던 2례의 환아중에서 잔여 효소가 전혀 없는 LNS로 사망한 1례와 잔여 효소가 부분적으로 존재하는 1례의 11년간 비교 추적 관찰한 결과를 보고한다. 증례 1: 핑크색 기저귀로 병원에 내원하여 반복적인 구내염으로 치료를 받다가 2개월에 경련발작으로 시작하여 심한 단백질 식품 거부, 발달지연, 퇴행이 있어 뇌성마비로 재활치료를 받던 중 만 6세에 LNS로 진단되어 요산치료로 요산은 정상화 되었으나 심한 불면증과 변비가 관찰되었다. 자해 행동과 척추 측만증, 간질 대발작, 심한 경직을 동반하며 몸통 근육긴장 저하, 무도무정위 운동과 운동실조가 진행성으로 심해졌다. 체중이 줄고 심한 영양실조 상태와 콩팥 모양의 요로 결석, 반복적 재발성 폐렴으로 병원 치료를 받다가 11세에 갑자기 사망하였다. 유전자 검사 결과 반접합성 HPRT1 변종(c.151C>T(p.Arg51Ter))이 밝혀졌다. 요산 수치는 10.5 mg/dl(정상 범위: ~3.5-7.9), HPRT 활성도는 0.02 nmol/hr/spot (10-23.8 nmol/hr/spot)이었다. 증례 2: 핑크색 기저귀로 병원에 방문하여 요산이 높아진 것을 알게 되었고 단백질을 거부하는 식사 습관이 있으며 저체중 상태로 성장하였다. 초등학교에 다니는 정상적인 지능을 가지고 있었고 자해 증상은 전혀 관찰되지 않았으며 정기적인 신장 초음파 검사에서 전혀 요로결석 없이 추적관찰 되었다. 유전자 검사상 반접합성 HPRT1 변이체(c.35A>C(p.Asp12Ala))를 가지고 있었으며 요산 수치와 HPRT 활성도는 11 mg/dL, 0.56 nmol/hr/spot이었다. 신생아 시기 이후까지 핑크색 기저귀가 보이며 심한 단백질 거부, 신경학적인 문제, 및 신장 결석을 동반한 경우 LNS에 대한 감별이 필요하다. 의심이 될 경우 혈청 요산 수치, HPRT 효소 활성도, 그리고 분자 생물학적인 검사가 LNS의 예후를 예측하는데 도움이 될 수 있다.

List of abbreviations

HPRT: Hypoxanthine-guanidine phosphoribosyltransferase

LNS: Lesch-Nyhan syndrome

EEG: Electroencephalogram

MRI: Magnetic resonance imaging

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