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Nakashima, Kengo
Bo, Ryosuke
Awano, Hiroyuki
Nishiyama, Masahiro
Iijima, Kazumoto

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Clinical Notes

Frequent recurrence of pancreatitis in a patient with Leigh syndrome

Short title: Recurring pancreatitis in Leigh syndrome

Authors

Kengo Nakashima, M.D. (1), Ryosuke Bo, M.D., Ph.D. (1), Hiroyuki Awano, M.D., Ph.D. (1), Masahiro Nishiyama, M.D., Ph.D. (1), Kazumoto Iijima, M.D., Ph.D. (1)

Affiliations

(1) Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

Corresponding author

Ryosuke Bo, MD. PhD.

Department of Pediatrics, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

Tel: +81-78-352-6090

Fax: +81-78-352-6099

E-mail: ryobo@med.kobe-u.ac.jp

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Leigh syndrome (LS) is a severe progressive neurodegenerative disease with symmetric necrotic lesions in the basal ganglia and brainstem due to mitochondrial dysfunction. LS is characterized by highly variable clinical features, including neurological symptoms, cardiac failure, hepatic failure, muscle symptoms, and digestive organ symptoms (1). Although there are some reports of acute pancreatitis in mitochondrial disease patients (2), there are few reports of LS patients. Additionally, since a high rate of psychomotor developmental delay is observed with LS, patients often cannot complain of symptoms indicative of pancreatitis, such as abdominal pain (3). Herein, we report the case of a LS patient with recurrent pancreatitis, emphasizing on her clinical features at admission. The informed consent for this case report was obtained from the patient's parents.

The patient was born at term with a birth weight of 3,096 g to non-consanguineous healthy parents. During infancy, she showed seizures and was diagnosed with LS based on elevated lactate levels, brain magnetic resonance imaging findings, and genetic analysis (homoplasmic m.8993T>G variant). Treatment with antiepileptic drugs, including phenobarbital, zonisamide, and clobazam, and mitochondrial cocktail, including thiamine, riboflavin, cobalamin, ascorbic acid, ubiquinone, and levocarnitine, was initiated after confirmation of diagnosis. At age 1, tube feeding was initiated to address difficulties in oral intake. At age 10, tracheostomy was performed because of recurrent respiratory infections. At age 11, the patient presented with tachycardia, peripheral coldness, and diarrhea. Observing increased pancreatic enzyme levels and pancreatic enlargement without gallstones on computed tomography, we diagnosed acute pancreatitis. Duodenal tube feeding was initiated to prevent pancreatitis recurrence. Nonetheless, the patient had four to five episodes of pancreatitis

each year between the age of 11 and 13. At age 12, magnetic resonance cholangiopancreatography revealed no malfusion of the pancreaticobiliary ducts. Antiepileptic drugs were discontinued due to suspected drug-induced pancreatitis; however, recurrence continued. At age 13, she showed uncontrollable recurrent pancreatitis and started total parenteral nutrition. The patient's treatment plan shifted to palliative care, and she died at age 13, with symptoms indicative of pancreatitis.

We retrospectively analyzed the patient's clinical condition at each hospitalization. Since there are few studies reporting the normal range of heart rate in children with severe psychomotor developmental delay, the criteria for tachycardia in this study was based on the systematic review on the normal heart rate of healthy control by Fleming et al (4). As shown in Table 1, clinical findings were non-specific, and some admissions (numbers 3 and 5) were associated with no change in vital signs or clinical findings except tachycardia. Tachycardia was the most common symptom, observed at 10 of 13 admissions, and peripheral coldness, diarrhea, and paleness were observed eight, five, and four times, respectively. Fever was not observed at any admission. Detailed radiological findings are shown in supplement Table 1.

We present this case to illustrate two important points in the diagnosis and management of LS. First, acute pancreatitis is a possible complication that is often resistant to standard treatment and has a poor prognosis. Second, even in LS patients, tachycardia may be an effective marker for the development of pancreatitis.

This patient developed recurrent pancreatitis without structural abnormalities of the pancreatic bile duct, and management was extremely difficult, suggesting specific risk factors for pancreatitis in LS patients. Although there are some reports about frequent recurrence of pancreatitis in patients with chronic progressive

external ophthalmoplegia and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes with the same mitochondrial dysfunction as LS (1), few cases of pancreatitis associated with LS have been reported. The detailed mechanism of recurrent pancreatitis in LS patients remains unclear. Increased endoplasmic reticulum stress within pancreatic cells and the metabolic defect in exocrine pancreas cells, leading to decreased exocrine enzyme secretion, which could result in intracellular protease accumulation and activation, have been reported to possibly cause acute pancreatitis in patients with other mitochondrial disorders (5,6). Such a pathology may also occur in this case. Previous reports of mitochondrial-disorder recurrent pancreatitis note the difficulty to treat the condition, the inability to prevent recurrence, and the poor prognosis, as was observed in our case.

Although the most common symptom of acute pancreatitis has been reported to be abdominal pain (7), severely disabled patients could not complain of it. Compared with other clinical findings, tachycardia was the most frequent symptom of acute pancreatitis in this patient, suggesting that tachycardia might substitute for pain complaint via reflecting an adrenergic response against severe pain. Therefore, attending clinicians should focus on monitoring the heart rates of LS patients without any other abnormal clinical findings to detect the development of pancreatitis.

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Author Contributions

K.N. collected the data and wrote the manuscript. R.B. reviewed and supervised the manuscript. H.A., M.N. gave technical support and conceptual advice. K.I. performed the critical revision of the manuscript. All authors read and approved the final manuscript.

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Table 1. Detailed clinical and biological data recorded at each of the 13 admissions for acute pancreatitis

Number of admission	Age at admission	Days of hospitalization (days)	Vital signs		Clinical findings				Biological findings	
			Fever (>38.0℃)	Tachy Cardia (*)	Palenes s	Peripheral coldness	Abdominal bloating	Diarrhea	Amylase (U/L)	Lipase (U/L)

1	11y3m	27	No	No (111)	Yes	Yes	No	Yes	1924	5816
2	11y6m	20	No	Yes (132)	Yes	Yes	No	Yes	917	837
3	11y10m	12	No	Yes (116)	No	No	No	N. A.	913	2078
4	11y10m	55	No	No (111)	No	No	No	No	1440	5036
5	12y2m	13	No	Yes (112)	No	No	No	No	696	2816
6	12y5m	10	No	Yes (120)	Yes	No	No	Yes	304	1027
7	12y9m	9	No	Yes (115)	Yes	Yes	No	N. A.	444	1691
8	12y10m	19	No	Yes (120)	No	Yes	Yes	Yes	650	2570
9	12y11m	11	No	Yes (114)	N. A.	Yes	No	N. A.	223	820
10	13y0m	12	No	Yes (112)	No	Yes	Yes	N. A.	629	2735
11	13y1m	14	No	No (83)	No	No	No	Yes	367	1736
12	13y2m	21	No	Yes (113)	No	Yes	No	N. A.	589	3171
13	13y4m	55	No	Yes (120)	No	Yes	No	N. A.	520	2530
									(RR: 37-125)	(RR: 17-57)

Abbreviations: y, year; m, month; N. A., not available; RR, reference range

(*) Tachycardia was defined as heart rate of >115 bpm for 8-11 years and of >108 bpm for 12-15 years, according to the study by Fleming et al.

Supplement table.1 Radiological data recorded at each of the 13 admissions for acute pancreatitis

Number of admission	Details of contrasted CT findings	CT Grade (JSS)	Echography findings
1	Necrosis of the pancreatic body Progression of inflammation beyond lower pole of kidney	Grade 2	N.D
2	Localized progression of inflammation around the pancreatic body and tail	Grade 1	N.D
3	Slight enlargement of the pancreas	Grade 1	N.D
4	Enlargement of the pancreas Progression of inflammation beyond lower pole of kidney	Grade 2	N.D
5	N.D	-	compatible
6	N.D	-	not evaluate the pancreas*
7	N.D	-	N.D
8	No abnormal findings	-	N.D
9	N.D	-	not evaluate the pancreas*
10	N.D	-	compatible
11	N.D	-	
12	N.D	-	
13	Localized enlargement of the pancreatic head Small amounts of Ascites	Grade 1	not evaluate the pancreas*

Abbreviations: N.D., not done; JSS, The JPN Severity Score

* : This patient has large amount of intestinal gas and severe scoliosis; therefore, echography was not able to evaluate the pancreas adequately.