

Original Article

Management of neonatal cow's milk allergy in high-risk neonates

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Abstract *Background:* We conducted a multicenter clinical survey to clarify the current attitudes to diagnosis or treatment of neonatal milk allergy (NMA) in institutions providing medical care for high-risk neonates in Japan.

Methods: Questionnaires were distributed to 263 institutions that provide medical care for high-risk infants. Information was requested on the number of hospitalized neonates between January 2004 and December 2005, the number of neonates diagnosed with milk allergy, frequent clinical symptoms, and clinical tests performed routinely when NMA was suspected.

Results: Responses were received from 145 institutions (55.1%). Of 69 796 hospitalized neonates, a diagnosis of cow's milk allergy was made in 0.21%. The incidence in infants with birthweight <1000 g was 0.35%. Gastrointestinal symptoms were identified as the most frequent symptoms that suggested NMA by 80% of institutions. A challenge test in each suspected case was performed in only 15% of institutions, even though it was considered to be the most significant test for diagnosis. Most institutions considered a specific immunoglobulin E test in cases of suspected NMA, but only one-third agreed on its diagnostic significance. A lymphocyte stimulation test was performed in only 5.5% of institutions.

Conclusions: This study is the first to show the incidence of NMA in institutions providing medical care for high-risk neonates in Japan. Current clinical tests may be insufficient for diagnosis of NMA in which non-immunoglobulin-E-mediated delayed allergic reactions are involved. Therefore, awareness of the clinical features of this disorder is required among neonatologists and allergists.

Key words diagnosis, food protein-induced enterocolitis syndrome, incidence, milk allergy, neonates.

In recent years several cases of neonatal milk allergy (NMA) in low birthweight infants have been reported in Japan, presenting with a variety of gastrointestinal, respiratory and cutaneous symptoms in the early neonatal period. However, the clinical features of NMA have not been clarified and well-defined diagnostic criteria are not established in current neonatal care in Japan. Although non-immunoglobulin (Ig) E mediated delayed type allergic reactions are thought to play a role in the majority of cases of NMA, methods to detect this type of reaction are also unavailable.

Powell and Sicherer *et al.* have described adverse reactions to cow's milk protein as food protein-induced enterocolitis syndrome (FPIES).^{1,2} FPIES is a type of adverse reaction to cow's milk protein in early infancy, which presents with gastrointestinal symptoms such as vomiting, diarrhea and bloody stools, and is typically negative in a skin prick test and IgE antibody test against milk proteins. Diagnostic criteria for FPIES consist of challenge tests against causal foods, similarly to other types of food allergy. However, such tests may be dangerous in neonates,

making the practicality of these criteria uncertain, and well-defined and safe diagnostic criteria in neonates are required.

In Japan, neonates with suspected milk allergy are usually admitted to institutions that provide medical care for high-risk neonates, such as neonatal intensive care units, and most are treated by neonatologists, rather than allergists. However, epidemiological investigations in a large population of infants with milk allergy have not been conducted. In this study, we performed a multicenter clinical survey with the aim of clarifying the current attitudes to diagnosis and treatment of neonatal milk allergy in high-risk neonates in Japan.

Methods

Questionnaires were distributed to 263 institutions certified by the Japan Society of Perinatal and Neonatal Medicine, including most of the major neonatal intensive care units (NICUs) in Japan. Diagnostic criteria for cow's milk allergy were not proposed in the questionnaire; therefore, the diagnosis of milk allergy was based on criteria at each institution. The questionnaire requested information on the number of hospitalized neonates between January 2004 and December 2005, the number of neonates diagnosed with cow's milk allergy, the diagnostic criteria used in the institution, clinical symptoms that were frequently seen, and clinical tests performed routinely when NMA was suspected. As the study was performed as a questionnaire-based survey, the

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amount of data that could be collected for individual cases was limited. Data were analyzed using a χ^2 -test and a P value <0.05 was considered statistically significant. Statistical analysis was performed using JMP version 4.05J. This study was approved by the Ethics Committee of Showa University School of Medicine.

Results

Incidence of NMA

Responses were received from 145 (55.1%) institutions, 53 (31.0%) of which had one or more neonate with cow's milk allergy in the preceding 2 years. The total number of hospitalized neonates in all institutions was 69 796 (mean $\pm$ standard deviation: 501.8 ± 282.4). Among these neonates, cow's milk allergy was diagnosed in 0.21% and the number of neonates with milk allergy per institution was 1.0 ± 2.0 . The incidence of NMA in infants with birthweight <1000 g was significantly higher than that in infants with birthweight 1500 g–2500 g. No significant differences in incidence were found among other bodyweight groups, but there was a tendency for a higher incidence of NMA with a lower birthweight (Table 1).

Diagnostic criteria for NMA

Of the responding institutions, 33% reported that they routinely used their own diagnostic criteria for NMA. About half of the institutions (47%) with at least one NMA case used their own criteria, compared to a quarter of those that had no NMA cases.

Clinical symptoms suggesting NMA

Gastrointestinal symptoms were selected by 80% of the institutions as most frequently suggestive of NMA, and of these symptoms bloody stool and diarrhea were selected by more than 30% of participants (Fig. 1). In ranking of symptoms, more than 50% of institutions selected bloody stool, diarrhea and vomiting as the first, second and third most common symptoms, respectively. However, some institutions considered non-specific symptoms such as failure to thrive, not doing well, and eruptions to be of more importance (Fig. 2). There were no differences in these data between institutions with one or more NMA cases compared to those with no NMA cases.

Clinical tests and diagnostic significance

Elimination tests for causal antigens, specific IgE and non-specific IgE, and tests for stool occult blood and fecal eosinophils were performed by several institutions in all cases of suspected NMA, and more than 80% of institutions routinely considered performing these tests (Fig. 3). A challenge test against cow's milk antigen was carried out for every suspected case in only

Table 1 Incidence of neonatal milk allergy (NMA)

Birthweight	Hospitalized infants	NMA	(%)
<1000 g	4034	14	0.35
1000–1500 g	5848	11	0.19
1500–2500 g	26 294	45	0.17
>2500 g	33 620	75	0.22
Total	69 796	145	0.21

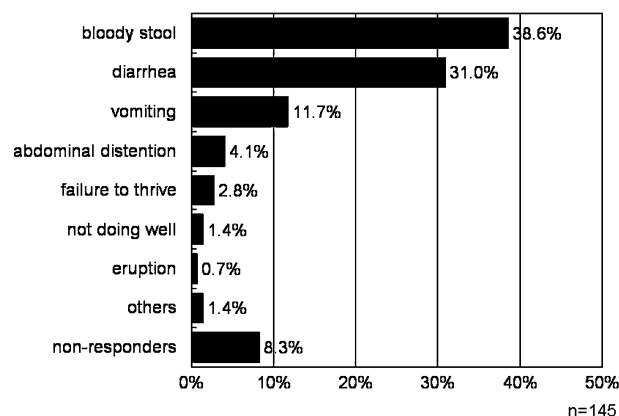


Fig. 1 Symptoms regarded as most frequent in cases of neonatal milk allergy.

15% of institutions, and the test was considered in only 70% of institutions, including those that performed a challenge test on a case-by-case basis. Only 5.5% of institutions routinely performed a lymphocyte stimulation test (LST) for every case. A comparison of institutions with or without NMA cases showed no significant differences in the proportion of institutions performing a specific IgE test, measurement of fecal eosinophils, and an LST. The proportion of institutions that performed a non-specific IgE test on a case-by-case basis was significantly higher in institutions with NMA cases (94.3%) than in those without NMA cases (82.6%). In contrast, the proportion of institutions that performed a skin prick test on a case-by-case basis was significantly higher in institutions without NMA cases (23.9%) than in those with NMA cases (5.7%).

The elimination test and challenge test were considered to be most significant for diagnosis of NMA, followed by food-specific IgE, fecal eosinophils and LST, respectively (Fig. 4). In ranking the clinical tests, most institutions chose the elimination and challenge tests to be of most importance, followed by measurements of fecal eosinophils and specific IgE (Fig. 5). There were no significant differences among tests thought to be of most significance between institutions with or without NMA cases or between those with or without their own diagnostic criteria.

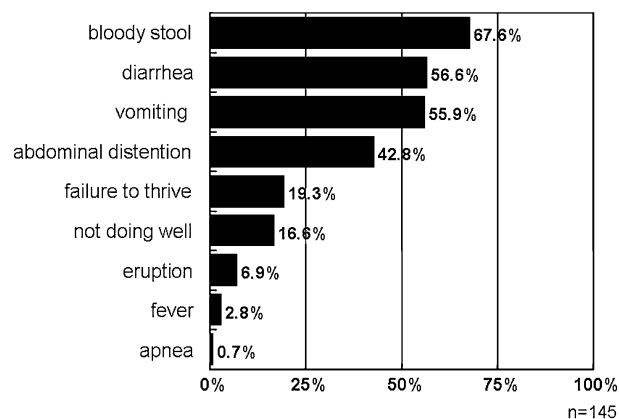


Fig. 2 Ranking of frequency of symptoms by responding institutions.

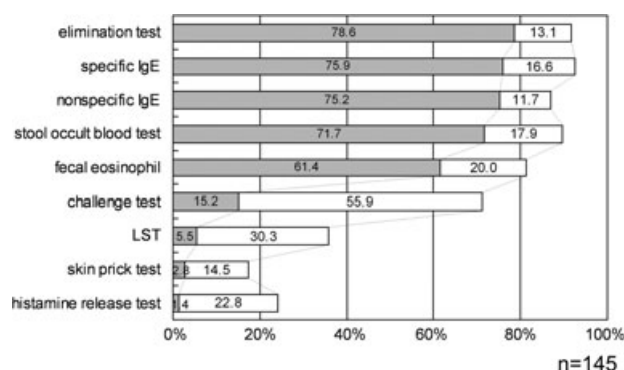


Fig. 3 Clinical tests performed in infants suspected to have neonatal milk allergy. (■) all cases; (□) case-by-case; IgE, immunoglobulin E; LST, lymphocyte stimulation test.

Discussion

The incidence of cow's milk allergy in infancy has been reported to range from 1.8% to 7.5%.³⁻⁷ This wide range is partly due to the lack of a definition or well-defined diagnostic criteria for milk allergy, and also because most studies have not been carried out prospectively. Recent studies suggest that the incidence of cow's milk allergy more appropriately ranges from 2 to 2.5%.⁶⁻⁷

There are few cases of NMA in Japan and the majority of these cases are treated by neonatologists, rather than allergists. Therefore, clinical investigation of a large population of patients with NMA has not been conducted. Host *et al.* reported that 1.4% (25/1749) of infants had an onset of cow's milk allergy within 4 weeks after birth, and that 64% of these infants developed milk allergy during their first year of life.⁷ However, the incidence of cow's milk allergy in neonates born in Japan and the incidence in low birth infants is unknown. This study is the first to examine the incidence of NMA in institutions that provide medical care for high-risk newborn infants, with the results based on independent diagnosis of NMA at each institution as well-defined diagnostic criteria common to all institutions have not been developed.

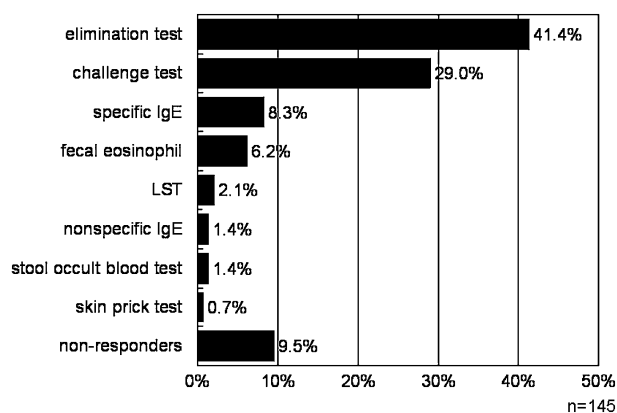


Fig. 4 Clinical tests regarded to be of diagnostic significance for neonatal milk allergy. IgE, immunoglobulin E; LST, lymphocyte stimulation test.

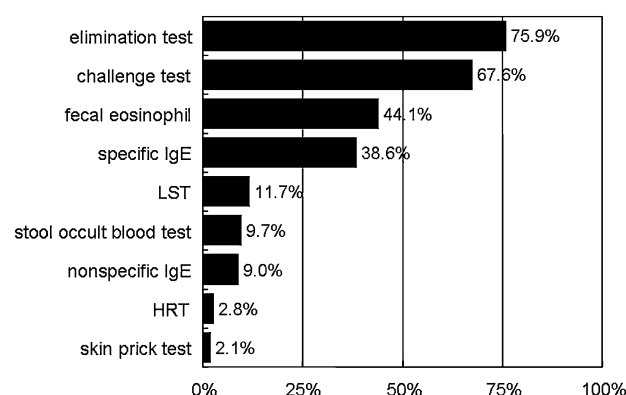


Fig. 5 Ranking of clinical tests used for diagnosis of neonatal milk allergy. HRT, histamine release test; IgE, immunoglobulin E; LST, lymphocyte stimulation test.

In this study, the incidence of NMA in infants with birthweight <1000 g was higher than that for other birthweight groups. Robertson *et al.*⁸ reported that preterm neonates, particularly those of less than 33 weeks' gestation, had higher serum concentrations of beta-lactoglobulin than term neonates, and suggested that the ability of the gastrointestinal tract to exclude antigenically intact food proteins increased with gestational age. Although the causal relationship between birthweight and the incidence of NMA is unknown, functional or immunological immaturity of the gastrointestinal tract in low birthweight infants may contribute to the development of NMA.⁹⁻¹¹

Various cutaneous and respiratory symptoms have been reported in NMA, in addition to gastrointestinal symptoms.^{6,7,12} In this study, most institutions reported gastrointestinal symptoms, especially diarrhea, bloody stool, vomiting and abdominal distention, to be the most common in NMA cases. In neonates with severe gastrointestinal symptoms such as bloody stool, milk allergy must be differentiated from conditions such as malrotation of the intestine, necrotizing enterocolitis and Hirschsprung disease, for which emergency surgical treatment may be needed.¹³⁻¹⁶ Few institutions reported frequent respiratory or cutaneous symptoms, which suggests that the pathology of NMA differs from IgE-mediated immediate allergic reactions to food, which are common in young children. Some institutions chose failure to thrive or not doing well as important symptoms for identifying possible NMA. Independent of these symptoms, liver dysfunction with elevation of liver enzymes such as aspartate aminotransferase and alanine aminotransferase has been reported in NMA.¹⁷ Therefore, in cases with liver dysfunction in which the patient shows a failure to thrive or is not doing well, differentiation of milk allergy from gastrointestinal diseases, infections and metabolic diseases is required.

In this study, 70% of institutions reported that they routinely test for specific IgE and non-specific IgE in cases of suspected NMA, but few believed that the diagnostic significance of these tests was high. Tests for specific/non-specific IgE are commonly performed as historically it has been believed that IgE-mediated reactions are involved in NMA, as well as in food allergy in young children. However, Host *et al.*⁷ reported that 40% of infants with cow's milk allergy are non-IgE-mediated, and in the

neonatal period non-IgE-mediated reactions may be more frequent in cow's milk allergy. In FPIES, an IgE antibody to causal food is typically not detected and the test is not necessarily required in all cases.^{1,2} However, infants with atypical FPIES and detectable IgE antibodies may be less likely to develop tolerance to cow's milk with age,^{2,18} and therefore an IgE test may be useful to predict the prognosis of NMA.^{7,19,20}

The lymphocyte stimulation test (LST) can be used for detection of non-IgE-mediated delayed type allergic reactions.^{21,22} Kimura *et al.* proposed that measurement of lymphocyte proliferation by flow cytometry may be useful in diagnosis of NMA,^{17,23} but this method is not available on a commercial basis and currently is not commonly used. It is also difficult to perform in all cases due to the concern of invasive stress in neonates caused by collection of a large blood sample, and further studies of this method are needed. A relatively large number of institutions reported performance of a stool test for eosinophils and considered that the diagnostic significance of this test was high. Eosinophil levels have been reported to reflect disease activity in milk allergy and to be useful for diagnosis and assessment of therapeutic effects.^{1,24} However, quantitative methods for measuring eosinophils are unavailable in most institutions, although measurement of fecal eosinophil granule-derived proteins, notably eosinophil-derived neurotoxin (EDN), may be a viable approach.^{25,26}

The institutional responses in this study indicated that tests that were easy to carry out and of low invasiveness were much more likely to be conducted, such as the CAP-radioallergosorbent test and measurement of fecal eosinophils. The challenge test with causal food is indispensable in diagnosis of food allergy, but is not realistic for all cases in newborn babies. Few institutions reported that they routinely carried out a challenge test with cow's milk for all cases of NMA; nearly half reported that they made this decision on a case-by-case basis. These findings suggest that guidelines for appropriate clinical tests in the diagnosis of NMA are needed for neonates, and especially for infants with birthweight <1000 g and those with severe complications.

To the best of our knowledge, this study is the first to reveal the incidence of NMA in institutions providing medical care for high-risk neonates in Japan. Various symptoms, but mainly gastrointestinal symptoms, are seen in neonates with milk allergy, and current clinical tests are insufficient for diagnosis of NMA in which non-IgE-mediated delayed allergic reaction plays a major role. Hence, NMA may be missed in some neonates, and therefore it is particularly important that both neonatologists and allergists are aware of the clinical features of this disorder. The possibility of milk allergy should always be considered in neonates exhibiting gastrointestinal symptoms.

References

- Powell GK. Food protein-induced enterocolitis of infancy: Differential diagnosis and management. *Compr. Ther.* 1986; **12**: 28–37.
- Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J. Pediatr.* 1998; **133**: 214–19.
- Halpern SR, Saller WA, Johnson RB, Anderson DW, Saperstein S, Reisch JS. Development of childhood allergy in infants fed breast, soy, or cow milk. *J. Allergy Clin. Immunol.* 1973; **51**: 139–51.
- Gerrard JW, MacKenzie JWA, Goluboff N. Cow's milk allergy: Prevalence and manifestations in an unselected series of newborns. *Acta. Paediatr. Scand. Suppl.* 1973; **234**: 3–21.
- Jacobsson I, Lindberg TA. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta. Paediatr. Scand.* 1979; **68**: 853–69.
- Bock SA. Prospective appraisal of complaints of adverse reactions to food in children during the first 3 years of life. *Pediatrics* 1987; **79**: 683–8.
- Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990; **45**: 587–96.
- Robertson DM, Pagenelli R, Dinwiddie R, Levinsky RJ. Milk antigen absorption in the preterm and term neonate. *Arch. Dis. Child.* 1982; **57**: 369–72.
- Weaver LT, Laker MF, Nelson R. Intestinal permeability in the newborn. *Arch. Dis. Child.* 1984; **59**: 236–41.
- Kuitunen OO, Savilahti E, Sarmesto A. Human alpha-lactalbumin and bovine beta-lactoglobulin absorption in premature and term infants. *Acta Paediatr. Scand.* 1989; **78**: 532–7.
- Sampson HA. Food Allergy. Part 1: Immunopathogenesis and clinical disorders. *J. Allergy Clin. Immunol.* 1999; **103**: 717–28.
- Wilson J. Milk intolerance: Lactose intolerance and cow's milk protein allergy. *Newborn Infant Nurs. Rev.* 2005; **5**: 203–7.
- Kubota A, Kawahara H, Okuyama H *et al.* Cow's milk protein allergy presenting with Hirschsprung's disease-mimicking symptoms. *J. Pediatr. Surg.* 2006; **41**: 2056–8.
- D'Netto MA, Herson VC, Hussain N. Allergic gastroenteropathy in preterm infants. *J. Pediatr.* 2000; **137**: 480–86.
- Sato T, Matsumoto Y, Watanabe N, Honda Y. A case of life-threatening milk allergy in a neonate who underwent laparotomy for suspected intestinal volvulus. *Jpn. J. Pediatr. Surg.* 2005; **37**: 604–7 (in Japanese).
- Hirose R, Yamada T, Hayashida Y. Massive bloody stools in two neonates caused by cow's milk allergy. *Pediatr. Surg. Int.* 2006; **22**: 935–8.
- Saito M, Obi M, Kimura M. Infantile hepatic dysfunction improved by elimination of cow's milk formulas. *Pediatr. Allergy Immunol.* 2005; **115**: 149–56.
- Sicherer SH. Food protein-induced enterocolitis syndrome: Case presentations and management lessons. *J. Allergy Clin. Immunol.* 2005; **115**: 149–56.
- Saarienen KM, Pelkonen AS, Makela MJ. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J. Allergy Clin. Immunol.* 2005; **116**: 869–75.
- Wood RA. The natural history of food allergy. *Pediatrics* 2003; **111**: 1631–7.
- Kondo N, Fukutomi O, Agata H *et al.* Proliferative responses of lymphocytes to food antigens are useful for detection of allergens in nonimmediate types of food allergy. *J. Invest. Allergol. Clin. Immunol.* 1997; **7**: 122–6.
- Hoffman KM, Ho DG, Sampson HA. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of allergy to cow's milk. *J. Allergy Clin. Immunol.* 1997; **99**: 360–66.
- Obi M, Okafuji I, Yoshida T, Saito M, Kimura M. Relationship of cell-mediated hypersensitivity with milk-induced Gastroenteropathy in infants. *J. Jpn. Pediatr. Soc.* 2003; **107**: 1361–6 (in Japanese).
- Hirano K, Shimojo N, Katsuki T, Ishikawa N, Kohno Y, Niimi H. Eosinophils in stool smear in normal and milk-allergic infants. *Jpn. J. Allergol.* 1997; **46**: 594–601 (in Japanese).
- Saitoh O, Kojima K, Sugi K *et al.* Fecal eosinophil granule-derived proteins reflect disease activity in inflammatory bowel disease. *Am. J. Gastroenterol.* 1999; **94**: 3513–20.
- Wada H, Horisawa T, Inoue M, Yoshida T, Toma T, Yachie A. Sequential measurement of fecal parameters in a case of non-immunoglobulin E-mediated milk allergy. *Pediatr. Int.* 2007; **49**: 109–11.