

Case Report

An Infantile Case of Transient, Severe Hypercholesterolemia with Normalization after Complete Weaning from Breast-feeding

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Abstract. A 20-d-old boy was referred to our department because of hyperthyrotropinemia at neonatal mass screening and diagnosed with neonatal transient hyperthyrotropinemia. A follow-up examination when the patient was 5 mo old revealed severe hypercholesterolemia. Familial hypercholesterolemia was first suspected because of the patient's significantly high levels of total and low-density lipoprotein cholesterol. The parent's serum lipid profiles were examined and found to be normal. He was completely breast-fed until 6 mo of age. Breast milk was still the main source of food for a period following weaning. At 14 mo old, the patient was weaned completely from breast milk, and his serum cholesterol levels decreased dramatically. According to the normal lipid profiles of the patient's parents and the spontaneous normalization of serum cholesterol levels after complete weaning from breast milk, breast-feeding was suggested to be responsible for his transient severe hypercholesterolemia. It is well documented that breast-fed infants have higher serum cholesterol levels than formula-fed infants. However, there is no reported case with severe hypercholesterolemia equivalent to or higher than the levels observed in the case of familial hypercholesterolemia. Although the exact mechanism is unknown, it is necessary to consider that a small number of cases develop severe hypercholesterolemia related to breast-feeding.

Key words: breast-feeding, infant, transient hypercholesterolemia

Introduction

High serum cholesterol levels represent a key risk factor in the development of

atherosclerosis, which may begin early in life and later progress to coronary heart disease. Recently, the screening of hypercholesterolemia during childhood has become more important because of the recent increases in the frequency of childhood obesity and metabolic syndrome. Among the causes of hypercholesterolemia, familial hypercholesterolemia (FH) can lead to asymptomatic, severe hypercholesterolemia even in the early months of life. It is especially important to screen infants for hypercholesterolemia during the early postnatal

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period.

Serum cholesterol levels during the early months of life are markedly influenced by the type of milk (1). Breast-fed infants rapidly develop higher total cholesterol (TC) levels than formula-fed infants during the first months of life, but the difference gradually diminishes before the age of 1 yr (2). It has been suggested that investigations to diagnose FH be deferred until approximately 1 yr of age when a diet consisting of formula and solid food is established (1). Breast milk is rich in cholesterol compared with formula and thus is likely to raise serum TC levels. Changes in serum TC levels are primarily due to levels of low-density lipoprotein cholesterol (LDL-C) (2). Although the exact mechanism is not clear, it has been reported that a few cases developed significant hypercholesterolemia that was related to breast-feeding as infants (1). However, there is no reported case of severe hypercholesterolemia with levels of serum TC and LDL-C equivalent to or higher than those observed in FH.

We report here the case of an infant who was breast-fed for the first year of life. This infant developed severe hypercholesterolemia that spontaneously normalized after complete weaning from breast milk.

Case report

Here, we present the case of a 20-d-old male at the time of his first visit to our department. He was the first child of nonconsanguineous parents and was born at 39 wk of gestation with a body weight of 2,768 g. After birth, he was breast-fed, and his rate of postnatal weight gain was normal. His TSH level was high (13 μ U/ml) at a neonatal mass screening performed when he was 5 d old. Re-examination when he was 12 d old revealed high levels of TSH. Therefore, he was referred to our department at 20 d of age. There was no thyroid or cardiovascular disease in his family history. Although his paternal grandfather had hypercholesterolemia that was under treatment with medication, his parents

had never been diagnosed as hypercholesterolemic.

At his first visit to our department, he was 52.0 cm tall and weighed 3,450 g and had a normal rate of weight gain. He was in good general condition, and further physical examination revealed no abnormalities, particularly no goiter and no cutaneous xanthoma. At his first examination, peripheral blood and biochemical examinations did not reveal any abnormalities. The patient's serum TC level was normal at 171 mg/dl. A thyroid functional examination revealed that the TSH level had already decreased to a normal range. Although the serum level of human thyroglobulin (HTG) was slightly elevated, serum levels of Free-T3 and Free-T4 were within the normal range (TSH, 4.30 μ U/ml; Free-T3, 5.70 pg/ml; Free-T4, 1.60 ng/dl; HTG, 148 ng/ml). Roentgenography of the knee joints revealed the existence of a distal femoral epiphysis. Ultrasonography revealed that his thyroid gland was of normal size and position. Based on these data, he was diagnosed with neonatal transient hyperthyrotropinemia. Continuous follow-up without replacement therapy was recommended.

His thyroid functional examination yielded normal results, and the HTG level decreased to a normal level when he was 3 mo old. However, his laboratory data revealed a high level of TC, with levels of 297 mg/dl at 3 mo of age and 547 mg/dl at 5 mo of age. Therefore, we investigated his lipid profile when he was 5 mo of age (Table 1). His serum lipid profile showed severely elevated levels of TC (522 mg/dl) and LDL-C (412 mg/dl), and his levels of HDL-C and triglyceride (TG) were normal. His apolipoprotein A-I and A-II levels were within normal ranges, and his apolipoprotein B level was elevated to 264 mg/dl. His apolipoprotein E phenotype was E3/E3, and the activity of the LDL receptor was 70% as determined by a lymphocyte assay. Although we investigated his parents' serum lipid profiles to rule out FH, their serum levels of TC, LDL-C, HDL-C and TG were all normal (father and mother: TC, LDL-C, HDL-C, TG and

Table 1 Laboratory data at 5 mo old

| | |
|----------------------------|--------------------------|
| Complete blood count | |
| WBC | 6,900 /ml |
| Hb | 12.6 g/dl |
| Ht | 36.9% |
| Plt | 29.7×10 ⁴ /ml |
| Blood chemistry | |
| AST | 75 IU/l |
| ALT | 48 IU/l |
| LDH | 314 IU/l |
| CK | 259 IU/l |
| BUN | 8 mg/dl |
| Cr | 0.3 mg/dl |
| Na | 137 mEq/l |
| K | 4.1 mEq/l |
| Cl | 109 mEq/l |
| Serum lipid profile | |
| TC | 522 mg/dl |
| LDL-C | 412 mg/dl |
| TG | 207 mg/dl |
| HDL-C | 55 mg/dl |
| Apolipoprotein A-I | 132 mg/dl |
| Apolipoprotein A-II | 25.6 mg/dl |
| Apolipoprotein B | 264 mg/dl |
| Apolipoprotein E phenotype | E3/E3 |
| LDL receptor activity | 70% |
| Thyroid function | |
| TSH | 4.30 μU/ml |
| T3 | 2.12 ng/ml |
| T4 | 12.20 μg/dl |
| Free-T ₃ | 5.70 pg/ml |
| Free-T ₄ | 1.60 ng/dl |
| HTG | 148 ng/ml |

Apolipoprotein B levels of 196 mg/dl and 183 mg/dl, 108 mg/dl and 108 mg/dl, 68 mg/dl and 72 mg/dl, 98 mg/dl and 94 mg/dl and 78 mg/dl and 72 mg/dl, respectively).

Figure 1 shows the subsequent changes in his serum lipid profile. The American Academy of Pediatrics released recommendations in 2008 for the management of hypercholesterolemia. In children who are more than 2 yr old, dietary therapy is indicated. Drug therapy should be considered in children older than 8 yr of age with

LDL-C levels higher than 190 mg/dl, with LDL-C levels of 160 mg/dl in combination with a family history of premature ischemic heart disease or with two or more risk factors (3). Due to his age, we started continuous follow-up without diet or drug therapy. During this period, he was completely breast-fed until 6 mo of age. He started solid food at 6 mo of age, but his level of intake was low, and breast milk was relied upon heavily to supplement his diet. At 12 mo of age, his intake of weaning food gradually increased, and the transition to solid food was smooth. Therefore, complete weaning from breast milk was conducted at 14 mo of age. His serum levels of TC and LDL-C remained at approximately 500 mg/dl and 400 mg/dl, respectively, until 12 mo of age. After complete weaning from breast milk, his serum levels of TC and LDL-C dramatically decreased. These levels normalized completely at 2 yr of age (TC, 184 mg/dl; LDL-C, 112 mg/dl). The level of apolipoprotein B also decreased to a normal range in association with the normalization of TC and LDL-C levels. The patient is now 5 yr old. We continue with periodic follow-up examinations of his thyroid and lipid profiles, both of which remain normal.

Discussion

Hypercholesterolemia is subdivided into two categories: primary hypercholesterolemia and secondary hypercholesterolemia. To diagnose the condition, the causes of secondary hypercholesterolemia, which include anemia, hypothyroidism, liver disease, malabsorption or malnutrition, acute or chronic infection, diabetes and the use of some drugs, should be ruled out. In our case, the patient's physical examination and laboratory data showed no sign of secondary hypercholesterolemia. Our patient showed a transient hyperthyrotropinemia during the infantile period; however, his thyroid function was normal continuously. Therefore, we suggested that his transient hyperthyrotropinemia was not related to his transient hypercholesterolemia.

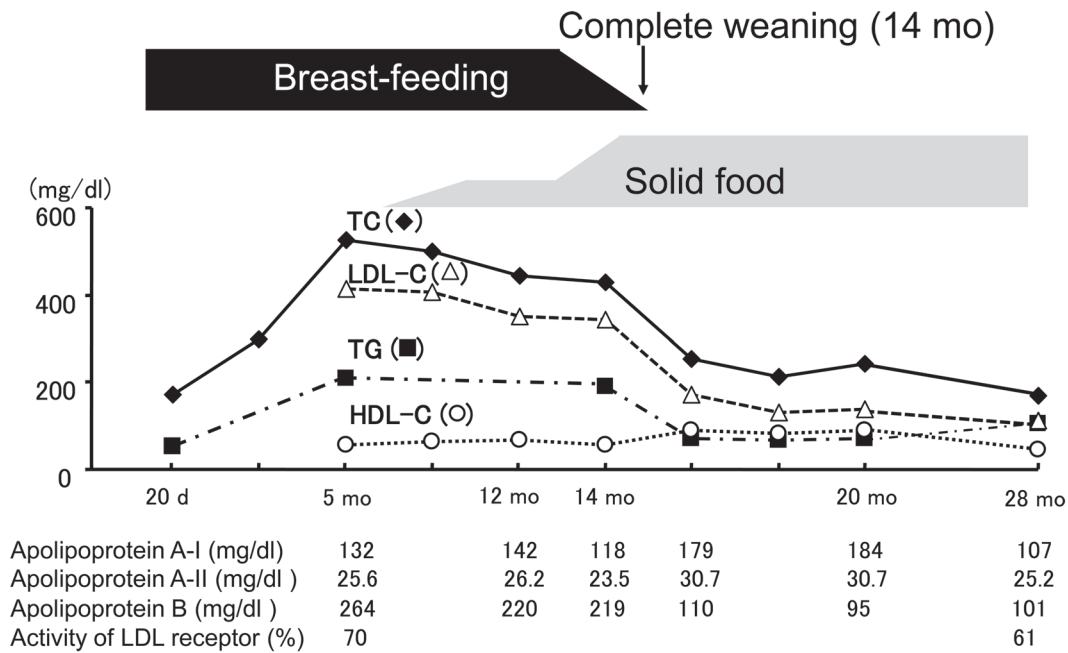


Fig. 1 Subsequent changes in his serum lipid profile.

Occurrence of hypercholesterolemia in transient hyperthyrotropinemia has not been reported to date. The causes of primary hypercholesterolemia include genetic mutations in the pathways of cholesterol absorption, biosynthesis or metabolism, including FH. FH is a disease caused by a mutation of the LDL receptor (4). In the homozygous state, atherosclerosis progresses rapidly, producing cardiovascular disease within the first two decades of life (4). A TC level of over 1,000 mg/dl and cutaneous xanthomas are common symptoms. In the heterozygous state, the TC level reaches 300–450 mg/dl, and hypercholesterolemia is usually the only clinical finding in the patient's first decade of life. However, hypercholesterolemia and atherosclerotic changes originate during the early postnatal period (5). Our case was first suspected to be heterozygous FH because of the patient's significantly elevated levels of TC and LDL-C (over 500 mg/dl and 400 mg/dl, respectively). However, the normal serum lipid profiles observed for the patient's parents and his clinical course of spontaneous normalization

after complete weaning from breast milk indicated that breast-feeding was responsible for his severe hypercholesterolemia. It has been reported that there is reduced activity of the LDL receptor to less than 50% of the baseline in cases of heterozygous FH (6). Although there are no data about the normal ranges in children, LDL receptor activity was 70% of the baseline in our case, as determined by a lymphocyte assay. This was not a significant reduction.

Table 2 shows the serum TC and LDL-C levels reported for the breast-fed, formula-fed and cholesterol-laden formula-fed infants in previous studies. It is well documented that breast-fed infants have higher serum TC levels than formula-fed infants (7–11). While there is no apparent difference between formula-fed and breast-fed infants by 1 mo of age, at 2 mo of age, there is a significant difference in the serum TC levels between these two groups. This difference persists until 8 mo of age and is not observed among infants who are 12 mo of age. Some studies investigated the LDL-C levels with TC and reported that the patterns observed for

Table 2 Reported serum TC and LDL-C levels of the breast-fed, formula-fed and cholesterol-laden formula-fed infants

| Authors and Year | Subjects | TC | | LDL-C | |
|--------------------------------|-----------|---------------------|----------------------------------------|----------------|---------------------------------------|
| | | Breast-fed | Formula fed | Breast-fed | Formula fed |
| Kallio <i>et al.</i> 1992 | 1 mo old | 58.3 ± 24.0 (n=33) | 57.9 ± 16.6 (n=13) | | |
| | 2 mo old | 146.7 ± 31.3 (n=31) | 112.4 ± 17.4 (n=14) | | |
| | 4 mo old | 150.8 ± 32.8 (n=31) | 126.8 ± 15.4 (n=14) | | |
| | 6 mo old | 154.8 ± 36.3 (n=29) | 136.7 ± 21.2 (n=16) | | |
| | 9 mo old | 172.2 ± 28.2 (n=33) | 159.8 ± 29.7 (n=13) | | |
| | 12 mo old | 188.4 ± 30.1 (n=7) | 170.3 ± 26.2 (n=7) | | |
| Agostoni <i>et al.</i> 2002 | 4 mo old | 171 ± 48 (n=15) | 148 ± 26 (n=23) | 95 ± 41 (n=15) | 73 ± 24 (n=23) |
| | | | 160 ± 28 (n=21) (cholesterol laden) | | 86 ± 29 (n=21) (cholesterol laden) |
| Bayley <i>et al.</i> 2002 | 4 mo old | 167 ± 9 (n=13) | 131 ± 9 (n=10) | 88 ± 9 (n=13) | 49 ± 10 (n=10) |
| | | | 148 ± 7 (n=9) (cholesterol laden) | | 68 ± 8 (n=9) (cholesterol laden) |
| | | | | | |
| Demmers <i>et al.</i> 2005 | 4 mo old | 157 ± 6 (n=18) | 126 ± 6 (n=8) | 80 ± 4 (n=18) | 46 ± 4 (n=8) |
| | | | 149 ± 6 (n=16) (cholesterol laden) | | 60 ± 4 (n=16) (cholesterol laden) |
| | | | | | |

LDL-C were similar to those observed for TC throughout these studies (8–11). The differences between breast-fed vs. formula-fed infants is assumed to be due to the fact that the cholesterol content of breast milk is greater than those of regular formulas (150 mg/l vs. 0–50 mg/l) (12). Recent studies have also investigated whether the supplementation of regular formula with cholesterol influences the serum TC and LDL-C levels compared with the levels in breast-fed infants (9–11). Interestingly, the infants that were fed regular formula supplemented with breast-milk levels of cholesterol showed an intermediate response. The serum TC and LDL-C levels were higher than in the infants that were fed regular formula, but they did not reach the levels observed in breast-fed infants. It is speculated that factors other than cholesterol intake account for the different cholesterol metabolisms observed between formula-fed and breast-fed infants. Although the detailed mechanism is unknown, some possible factors were suggested in previous studies. Individual fatty acids can affect cholesterol metabolism, which in turn affects serum lipoprotein

concentrations independent of the intake of dietary cholesterol (13). The fatty acid profile and content in breast milk are modified by the maternal diet (14) and vary throughout the feeding period. Certain factors in breast-milk such as hormones, immunoglobulins and nucleotides may increase the absorption of cholesterol in breast-fed infants (15). Recently, leptin, ghrelin, adiponectin and resistin have been detected in breast milk (16). These hormones are involved in the regulation of energy balance and lipid metabolism and may have a role in the regulation of lipid metabolism in the neonatal period and infancy, as well as long-term effects in adulthood. However, the relationship between these hormones in breast milk and cholesterol metabolism in the infantile period has not been reported. Future research is necessary to clarify the role of hormones present in breast milk.

Earlier studies, which were performed for the purpose of early FH screening, have reported on a few cases of significant hypercholesterolemia among breast-fed infants. Darmady *et al.* performed a longitudinal prospective study of serum TC levels during the first year of life in

302 healthy babies (1). At 4 mo of age, 15 infants had cholesterol levels over 240 mg/dl. In 2 infants, these values were over 300 mg/dl. At 1 yr of age, 5 children had concentrations above 240 mg/dl (1). Vobecky *et al.* found that among 556 infants in good health, 6.4% of infants at 6 mo of age and 7.3% of infants at 12 mo of age had serum TC levels above 200 mg/100 ml (17). The authors of these studies suggested that breast milk had a marked effect on those infants with significant hypercholesterolemia. However, there was no case that had a severe elevation of TC levels of over 500 mg/dl as was found in our case. Among breast-fed infants, the efficiency of cholesterol absorption from the gut may exhibit considerable individual variation at similar levels of cholesterol intake, which might be important in the regulation of hepatic cholesterol synthesis and LDL receptor activity. This may partially explain individual differences in serum TC levels in response to dietary cholesterol (18). An association between cholesterol absorption and the apolipoprotein E phenotype has been previously observed. Subjects with the E3/E4 phenotype were found to have more efficient cholesterol absorption and higher serum LDL-C levels than subjects with other apolipoprotein E phenotypes (19). In our case, the patient's apolipoprotein E phenotype was E3/E3 and is thought to be unrelated to his severe hypercholesterolemia.

The long-term effects of breast-feeding on blood cholesterol and on the risk of cardiovascular disease in later life have been examined previously (20, 21). Previous systematic reviews and meta-analyses have shown that the TC and LDL-C levels of breast-fed subjects, compared with those of formula-fed subjects, are slightly lower in adulthood (20, 21). The mechanistic basis for a programming effect of breast-feeding on adult cholesterol levels remains to be established, and there is little evidence that breast-feeding reduces an infant's risk of cardiovascular disease later in life. However, prolonged breast-feeding over 1 yr has been

related to higher levels of adult TC and LDL (22). In our case, long-term follow-up will be required to assess the effects of prolonged breastfeeding on lipid profiles in later adult life.

In conclusion, we studied an infantile case of transient severe hypercholesterolemia related to breast-feeding. Although the exact mechanism is unknown, it should be taken into consideration that very few cases develop severe hypercholesterolemia related to breast-feeding at the time of serum cholesterol level evaluation in infants. Breast-feeding is associated with increased TC and LDL-C levels in infancy but lower levels in adulthood. Long-term follow up will be necessary to evaluate the effects of breast-feeding on this patient's lipid profiles as an adult.

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