Dorfman-Chanarin Syndrome in a Turkish Kindred: Conductor Diagnosis Requires Analysis of Multiple Eosinophils

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Dorfman-Chanarin syndrome is a rare, autosomal recessive inherited lipid storage disease with congenital ichthyotic erythroderma due to an acylglycerol recycling defect. Demonstration of lipid vacuoles in neutrophils from peripheral blood smears (Jordans’ anomaly) in patients with ichthyotic erythroderma leads to the diagnosis. In spite of frequent liver, muscle, ear, eye and central nervous system involvement, Dorfman-Chanarin syndrome may present clinically as monosymptomatic ichthyosis. Here, we report clinical and laboratory investigations in a consanguineous family from Turkey with 3 affected family members, and demonstrate the lipid vacuoles in epidermal Langerhans’ cells for the first time. Langerhans’ cell phenotyping suggests that the skin inflammation is due to the gene defect and not to underlying atopic dermatitis. Microscopic examination of eosinophils for lipid vacuoles to identify conductors revealed variable percentages of normal and vacuolized eosinophils in conductors, suggesting the microscopic analysis of at least 10 eosinophils for conductor identification.

Key words: Jordans’ anomaly; congenital ichthyotic erythroderma; neutral lipid storage disease; Langerhans’ cell phenotyping; electron microscopy.

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CASE REPORTS

Case 1

A 16-year-old boy, who was already diagnosed as having Dorfman-Chanarin syndrome some months ago at our department (4), asked if we could also examine other members of his family who lived in France. He arranged a visit of the entire family at our department for clinical examination (Fig. 1). During this visit, 2 additional members of the family were diagnosed as having Dorfman-Chanarin syndrome, 6 of the 7 unaffected family members were diagnosed as conductors by vacuole demonstration in the eosinophils (Table I). Since the best method for conductor identification is still a matter of debate (5), this report focuses on clinical aspects of this family and the appropriate number of eosinophils to be investigated for conductor identification.

Table I. Laboratory analysis in a family with Dorfman-Chanarin syndrome (DCS)

| Patient no. | Eecc | Emic | Vac/e | CK | Notes |
|------------|------|------|-------|----|-------|
| III/2      | 3.0  | 2    | 5/10  | 53 | Evident conductor |
| III/5      | 1.9  | 0    | 2/10  | 28 | Evident conductor |
| III/6      | 1.4  | 2    | 6/10  | 30 | Evident conductor |
| IV/2       | 1.4  | 1    | 0/10  | 32 | Probably non-conductor |
| IV/4       | 2.5  | 3    | 4/10  | 46 | Conductor |
| IV/5       | 3.0  | 3    | 4/10  | nd | Conductor |
| IV/6       | 1.8  | 0    | 10/10 | 133| DCS, case 1 |
| IV/9       | 0.8  | 0    | 10/10 | 158| DCS, case 2 |
| IV/10      | 1.5  | 1    | 10/10 | 249| DCS, case 3 |
| IV/11      | 2.3  | 1    | 2/10  | 28 | Conductor |

Eecc: percentage of eosinophils determined by electronic cell counter; Emic: percentage of eosinophils determined by microscopic examination; Vac/e: number of eosinophils containing vacuoles/total number of analysed eosinophils; CK: creatinine kinase; nd: not done.
further reflecting the local inflammation induced by the inherited disorder of lipid metabolism. The FcεRI/FcγRII-ratio, known to be elevated in chronic atopic dermatitis lesions, was calculated from the respective rFI values as described. However, the low FcεRI/FcγRII-ratio of 0.6 did not suggest an underlying atopic dermatitis (8).

Case 2

A 16-year-old girl (Fig. 1, patient IV/9) of Turkish origin was born without skin abnormalities. At the age of 6 months she developed ichthyotic erythroderma. Her mother was known to be related to her husband some generations earlier, but the exact nature of consanguinity was unknown. The girl was attending a normal high school in France without problems.

A recent audiogram revealed no abnormality. Daily skin care with urea-containing emollients was necessary to maintain an acceptable skin status.

On physical examination, ichthyotic erythroderma with massive lichenification was found to be present on the entire body, including the flexural regions. Her palms showed hyperlinearity and there was a dark-brownish scaling on the back of her hands.

Normal laboratory values included GOT, GPT, gGT, lactate dehydrogenase, bilirubine, creatinine, cholesterine, triglycerides, HDL and LDL fraction. The creatinine kinase was raised to 158 U/l (10–80 U/l) and alkaline phosphatase to 737 U/l (475–617 U/l). Cell counter analysis of leukocytes and thrombocytes gave normal results, but microcytosis and hypochromasia of erythrocytes was detected. Examination of blood smears revealed lipid vacuoles in neutrophils, eosinophils and monocytes.

Case 3

Her brother, a 13-year-old boy (Fig. 1, patient IV/10), was born with ichthyotic erythroderma. According to his parents, he tended to develop blisters from mechanical friction more easily than other children and showed delayed wound healing. He was wearing glasses and was attending a normal high school in France without problems. At a height of 143 cm, he was one of the smallest boys in his class. His skin status had always been worse than his sister's.

On physical examination, an ichthyotic erythrodermic skin was covered with large ichthyosiform, dark-brownish to black scales. The palms showed hyperlinearity. Livedo reticularis and a few blisters were present on his legs. There was abnormal growth of the teeth. Despite daily applications of emollients, the dark ichthyosiform scales were refractory to treatment.

Normal laboratory values included GOT, GPT, gGT, lactate dehydrogenase, bilirubine, creatinine, cholesterine, triglycerides, HDL and LDL fraction. The creatinine kinase was raised to 249 U/l (10–80 U/l) and alkaline phosphatase to 1120 U/l (475–617 U/l). Cell counter analysis of erythrocytes, leukocytes and thrombocytes gave normal results. Examination of blood smears revealed lipid vacuoles in neutrophils, eosinophils and monocytes.

DISCUSSION

In 1974 Dorfman et al. (1) described a new subtype of congenital ichthyosiform erythroderma, which was delineated from other subtypes by lipid vacuoles in peripheral blood granulocytes. These lipid vacuoles were first described by

Fig. 1. Pedigree of the family with Dorfman-Chanarin syndrome with results of the leukocyte analysis and patient numbers.

Acta Derm Venereol 80
Jordans in 1953, (9) and are hence often referred to as Jordans’ anomaly (10). The independence of this new disease entity was soon confirmed by subsequent case reports from other countries (2, 11). The name “neutral lipid storage disease” was proposed for the new disease from Chanarin et al. (2). Today it is mostly referred to as Dorfman-Chanarin syndrome. Including this report, 32 patients have been described in the literature (Table II).

Dorfman-Chanarin syndrome may be defined as an autosomal recessive, congenital ichthyotic erythroderma with obligate deposition of cytoplasmic neutral lipid vacuoles in various cells of the human body, especially in keratinocytes and granulocytes (9). In addition, lipid inclusions were described until now in monocytes, mast cells, fibroblasts, megakaryocytes, pericytes, muscle cells and Schwann cells but not within lymphocytes, normoblasts, red blood cells and platelets (1, 12 – 14). These results could be confirmed by our investigations and beyond this we were able to demonstrate lipid droplets in epidermal Langerhans’ cells for the first time.

Extracutaneous manifestations of Dorfman-Chanarin syndrome may be present, such as hepatosplenomegaly with fatty liver degeneration, but mostly normal aminotransferases. Double-sided cataracts may be present in early childhood or develop later in life. Growth retardation may be present and particularly small, low-set ears are present, at least in the family described here. Despite the commonly raised muscle enzymes, muscle weakness is rarely observed. Neurological manifestations may include ataxia, bilateral neurosensory hearing loss and horizontal nystagmus (3). A defect of acylglycerol recycling from triacylglycerol to phospholipid has recently been identified in fibroblasts from patients with Dorfman-Chanarin syndrome (15), however, no single gene defect for this syndrome has been identified.

The differential diagnosis of Dorfman-Chanarin syndrome includes many, mostly rare, diseases with an ichthyotic

Fig. 2. Electron micrograph of keratinocytes in the basal layer (case 1). Multiple prominent lipid droplets (long arrows) within the cytoplasm of the keratinocytes are visible. Several intraepidermal situated lymphocytes without vacuoles are demonstrated (L). Basement membrane (short arrows) (×4,300).

Fig. 3. Electron micrograph of a dermal situated mast cell (m) and a fibroblast (f) with cytoplasmic lipid inclusions (arrows) (case 1) (×4,700).

Fig. 4. Electron micrograph of an intraepidermal situated Langerhans’ cell (case 1) with typical lipid vacuoles (arrows) and Birbeck granules (arrow heads) (×6,000).
Table. II. Synopsis of clinical features from all published patients with Dorfman-Chanarin syndrome

| No. | Reference | Age  | Sex  | Consanguinity | Neuromuscular symptoms | Creatinine kinase | Eye symptoms | Liver symptoms | Neuro-sensual deafness | Varia                      |
|-----|-----------|------|------|---------------|------------------------|------------------|--------------|---------------|----------------------|---------------------------|
| 1   | Rozenszajn (10) | 35 y | F    | Cousin 1'     | Yes                    | Normal           | Cataract     | ?             | Yes                   | Diabetes mellitus         |
| 2   | "          | 26 y | F    | No            | ?                      | ?                | None         | Yes           | Yes                   | Bowel involvement         |
| 3   | "          | 10 m | F    | No            | ?                      | ?                | ?            | ?             | ?                    | Bowel involvement         |
| 4   | "          | 7 d  | M    | No            | ?                      | ?                | ?            | ?             | ?                    | Bowel involvement         |
| 5   | "          | 6 m  | M    | No            | ?                      | None            | Yes          | ?             | ?                    | Bowel involvement         |
| 6   | Dorfman (1) | 21 y | M    | Cousin 1'     | No                     | ?                | None         | Yes           | No                    | Bowel involvement         |
| 7   | "          | 16 y | M    | No            | ?                      | None            | Yes          | No            | No                   | Bowel involvement         |
| 8   | Chanarin (2) | 22 y | F    | No            | Pathological           | None            | Yes          | No            | No                   | Collodion baby            |
| 9   | Miranda (11) | 41 y | M    | No            | Yes                    | None            | Yes          | Yes           | No                   | Collodion baby            |
| 10  | Angelini (19)| 5 y  | F    | No            | Pathological           | Cataract        | Yes          | No            | Bowel involvement     |
| 11  | Williams (17)| 46 y | M    | Cousin 1'     | Yes                    | Pathological     | Cataract     | ?             | Yes                   | Aortic insufficiency       |
| 12  | "          | 13 y | M    | Yes          | Yes                    | Pathological     | Cataract     | ?             | Yes                   | Small stature             |
| 13  | "          | 12 y | M    | Yes          | Yes                    | Pathological     | Cataract     | ?             | Yes                   | Small stature             |
| 14  | "          | 5 y  | F    | Yes          | Yes                    | Pathological     | Cataract     | Yes           | Yes                   | Intelligence reduction     |
| 15  | "          | 24 y | F    | Cousin 1'     | No                     | Normal           | ?            | Yes          | Yes                   | Intelligence reduction     |
| 16  | "          | 2 y  | M    | No            | Pathological           | None            | No           | No            | No                   | Bowel involvement         |
| 17  | Muscumecci (18)| 3 y  | M    | Cousin 1'     | No                     | Normal           | None         | Yes          | No                   | Collodion baby            |
| 18  | Wolf (5)   | 4 y  | M    | No            | No                     | Yes             | No           | ?            | ?                    | Collodion baby            |
| 19  | Venencie (22)| 19 y | M    | No            | Yes                    | None            | No           | Yes          | No                   | Collodion baby            |
| 20  | Nanda (20) | 14 y | M    | No            | ?                      | ?                | None         | No           | No                   | Collodion baby            |
| 21  | Venencie (22)| 14 y | M    | Yes          | No                     | Strabism         | Yes          | No           | No                   | Collodion baby            |
| 22  | "          | 15 y | F    | No            | ?                      | Cataract         | Yes          | ?            | ?                    | Nystagmus                  |
| 23  | Baňuls (13)| 52 y | F    | Cousin 1'     | No                     | Pathological     | Yes          | Yes          | Yes                   | Intelligence reduction     |
| 24  | Mela (23)  | 16 y | M ? | No            | Normal                | ?                | Yes          | No            | No                   | Intelligence reduction     |
| 25  | Wollenberg (4)| 16 y | M    | Cousin 1'     | No                     | Normal           | None         | Yes          | No                   | Small stature, small ears |
| 26  | Kakourou (16)| 8 y  | M    | No            | ?                      | Cataract         | Yes          | No           | No                   | Improvement on diet       |
| 27  | Kaasas (24)| 11 y | F    | No            | Normal                | Strabism         | Yes          | No           | No                   | Improvement on diet       |
| 28  | Srebrnik (14)| 18 y | M    | No            | Pathological           | No              | Yes          | No            | No                   | Improvement on diet       |
| 29  | "          | 21 y | M    | Cousin 2'     | No                     | Pathological     | Strabism     | Yes          | No                   | Improvement on diet       |
| 30  | Wollenberg (4)| 16 y | F    | Yes          | No                     | Pathological     | ?            | ?            | No                   | Improvement on diet       |
| 31  | "          | 13 y | M    | Yes          | No                     | Pathological     | ?            | ?            | No                   | Improvement on diet       |

y: years; m: months; d: days; F: female; M: male.

The phenotype. Lipid vacuoles inside keratinocytes and peripheral blood granulocytes are the diagnostic hallmark for Dorfman-Chanarin syndrome. Similar vacuoles are seen in another condition, the inherited phytanic acid storage disease named “heredopathia atactica polyneuritiformis” or Refsum’s disease. In contrast to the vacuoles found in Dorfman-Chanarin syndrome, lipid inclusions in Refsum’s disease can only be seen in the cytoplasm of keratinocytes and melanocytes.

At present there is no known causal therapy for Dorfman-Chanarin syndrome. Intensive symptomatic therapy with oil baths and emollients usually leads to acceptable improvement of the skin changes. A response of gastrointestinal symptoms and, to a lesser extent, muscle weakness to a gluten-free diet has been reported 17 years ago (11). More recently, a low-fat diet poor in long-chain and enriched with medium-chain fatty acids has been reported to improve liver function, liver size and skin manifestations in an 8-year-old boy (16).

The pathogenetic link from a disturbed lipid metabolism to the inflammatory skin phenotype is unknown at present. Since in Dorfman-Chanarin syndrome the diagnosis may be easily done by leukocyte analysis, this should be routinely performed in all cases of ichthyotic erythroderma. Electronic cell counters, frequently used for routine leukocyte analysis, are not suitable for detection of the lipid granules, since they will give false negative results (5, 17). Microscopic examination of blood smears must be performed.

A screening of the family members for conductors should be offered, based on clinical relevance and the need for genetic counselling. For conductor identification, microscopic examination of eosinophils has been reported to be useful (17, 18). However, this diagnostic aid has failed in some obligate heterozygotes (5). According to our eosinophil analysis data, this might have been due to the fact that not all of a conductor’s eosinophils do contain lipid vacuoles: the 6 conductors investigated from the family described here
revealed variable percentages of normal and vacuolized eosinophils (Fig. 5), with only 38% total and a minimum of 2/10 positive cells in their blood smears (Table I). Keeping in mind the low occurrence of eosinophils in a normal blood smear (2 – 4%), the number of 100 leukocytes analysed in a routine setting must be considered insufficient. On the other hand, the low number of eosinophils does not allow for a formal statistical analysis to be performed. Since in our family some conductors had only 2/10 positive eosinophils in their blood smears, we propose the analysis of at least 10 eosinophils as mandatory for a valid conductor investigation in Dorfman-Chanarin syndrome.

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REFERENCES

1. Dorfman ML, Hershko C, Eisenberg S, Sagher F. Ichthyosiform dermatosis with systemic lipidosis. Arch Dermatol 1974; 110: 261 – 264.
2. Chanarin I, Patel A, Slavin G, Wills EJ, Andrews TM, Stewart G. Neutral-lipid storage disease: a new disorder of lipid metabolism. BMJ 1975; 1: 553 – 555.
3. Traupe H. The Ichthyoses. Berlin Heidelberg New York: Springer, 1989: 189 – 192.
4. Wollenberg A, Schaller M, Röschinger W, Schirren CG, Wolff H. Dorfman-Chanarin-Syndrom. Eine Neutrallipid-Speicherkrankheit. Hautarzt 1997; 48: 753 – 758.
5. Wolf R, Zaritzky A, Pollak S. Value of looking at leucocytes in every case of ichthyosis. Dermatologica 1988; 177: 237 – 240.
6. Wollenberg A, Wen S, Bieber T. Phenotyping of epidermal dendritic cells—clinical applications of a flow cytometric micro-method. Cytometry 1999; 37: 147 – 155.
7. Wollenberg A, Kraft S, Hanau D, Bieber T. Immunomorphological and ultrastructural characterization of Langerhans cells and a novel, inflammatory dendritic epidermal cell (IDEC) population in lesional skin of atopic eczema. J Invest Dermatol 1996; 106: 446 – 453.
8. Wollenberg A, Wen S, Bieber T. Langerhans cell phenotyping: A new tool for differential diagnosis of inflammatory skin diseases. Lancet 1995; 346: 1626 – 1627.
9. Jordans GH. The familial occurrence of fat-containing vacuoles in the leukocytes diagnosed in two brothers suffering from dystrophia musculorum progressiva. Acta Med Scand 1953; 146: 419 – 424.
10. Rozenszajn L, Klajman A, Yaffe D, Efrati P. Jordans’ anomaly in white blood cells. Blood 1966; 28: 258 – 265.
11. Miranda A, DiMauro S, Eastwood A, Hays A, Johnson WG, Olarte M, et al. Lipid storage myopathy, ichthyosis and steatocerebro muscular neuropathy. Muscle Nerve 1979; 2: 1 – 13.
12. Szebrzik A, Tur E, Perlik C, Elman M, Messer G, Ilie B, et al. Dorfman Chanarin syndrome: a case report and a review. J Am Acad Dermatol 1987; 17: 801 – 808.
13. Bähls J, Betloch I, Botella R, Sevila A, Morell A, Roman P. Dorfman-Chanarin syndrome (neutral lipid storage disease). A case report. Clin Exp Dermatol 1994; 19: 434 – 437.
14. Szebrzik A, Brenner S, Ilie B, Messer G. Dorfman-Chanarin syndrome: morphologic studies and presentation of new cases. Am J Dermatopathol 1998; 20: 79 – 85.
15. Igal RA, Coleman RA. Acylglycerol recycling from tricacylglycerol to phospholipid, not lipase activity, is defective in neutral lipid storage disease fibroblasts. J Biol Chem 1996; 271: 16644 – 16651.
16. Kakourou T, Drogari E, Christomanou H, Giannouli A, Dacou Voutetakis C. Neutral lipid storage disease-response to dietary intervention. Arch Dis Child 1997; 77: 184.
17. Williams ML, Koch TK, O’Donnel J, Frost PH, Epstein LB, Grizzard WS, et al. Ichthyosis and neutral lipid storage disease. Am J Med Genet 1985; 20: 711 – 726.
18. Muscumeci S, D’Agata A, Romano C. Ichthyosis and neutral lipid storage disease. Am J Med Genet 1988; 29: 377 – 382.
19. Angelini C, Philipart M, Borrone C, Bresolin N, Cantini M, Lucke S. Multisystem triglyceride storage disorder with impaired long chain fatty acid oxidation. Ann Neurol 1980; 7: 5 – 10.
20. Nanda A, Sharma R, Kanwar AJ, Kaur S, Dash S. Dorfman-Chanarin syndrome. Int J Dermatol 1990; 29: 349 – 351.
21. Venencie PY, Pauwels C, Reik A, Mielot F, Hadchouel M, Odievre M. Ichthyose avec accumulation de lipides neutres: syndrome de Dorfman-Chanarin. A propos d’une observation familiale. Ann Dermatol Venerol 1993; 120: 758 – 760.
22. Venencie PY, Armengaud D, Fodés C, Vieillefond A, Coulombe L, Hadchouel M. Ichthyosis and neutral lipid storage disease (Dorfman-Chanarin syndrome). Pediatr Dermatol 1988; 5: 173 – 177.
23. Mela D, Artom A, Goretta R, Saragoni G, Riolfo M, Ardonino S, et al. Dorfman-Chanarin syndrome: a case with prevalent hepatic involvement. J Hepatol 1996; 25: 769 – 771.
24. Kaassis C, Ginies JL, Berthelot J, Verret JL. Le syndrome de Dorfman-Chanarin. Ann Dermatol Venerol 1998; 125: 317 – 319.