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ORIGINAL ARTICLE

Congenital dyserythropoietic anemia in a Chinese family with a mutation of the *CDAN1*-gene

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Abstract Congenital dyserythropoietic anemia I (CDA I) is a well-defined entity within the heterogeneous group of the CDAs. So far, most CDA cases were reported from Europe and Israel. A homozygous mutation of the *CDAN1*-gene was identified from a founder population observed in Bedouin tribes in Israel, and many different mutations in additional cases from Europe were reported. Few cases of CDA I were presented from Asian regions so far, mostly without convincing data and only one case in which a mutation of the *CDAN1*-gene was detected. Here, the first Chinese family with the typical hematological phenotype, osseous syndactyly and with a compound heterozygous *CDAN1*-gene mutation is described. Prevalence data of CDA I from Asian countries are not known, but experiences from Europe suggest that in many families the disorder remains undiagnosed.

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Introduction

Congenital dyserythropoietic anemia I (CDA I) is a well-defined entity within the heterogeneous group of the CDAs [7]. Ineffective erythropoiesis is the predominant mechanism of the anemia, and the diagnosis is based on characteristic dysplasias of the majority of polychromatic and oxyphilic erythroblasts, with internuclear chromatin bridges being a morphological hallmark of the disorder [9, 21]. Unique changes of the chromatin structure, confined to erythropoiesis are seen by electron microscopy [6, 22]. Heredity is autosomal recessive, and treatment with interferon α results in remission with disappearance of functional and morphological abnormalities of erythropoiesis and iron resorption [13] that is upregulated in untreated cases.

CDA I is a very rare disease. At present, 90 cases from 79 families were identified from published case reports, in addition to 30 unpublished cases collated in the German Registry on congenital dyserythropoietic anemias [8] and more than 70 cases from a founder population observed in a large Bedouin tribe [3]. A homozygous mutation of the *CDAN1*-gene coding for the protein codanin was detected in the latter population, and many different mutations were observed in the vast majority of families resident in Europe in whom the gene was sequenced.

Most families with CDA I were reported from European countries and an ongoing survey in Europe suggest that the alertness for this disease entity is responsible for the incidence rather than e.g., ethnicity. Very few families were reported from Asian regions, and with the exception of a

family from Polynesia [15, 19], there is no molecular proof of a correct CDA I-diagnosis.

Here, we report the first family observed in the People's Republic of China with the typical phenotype and a compound heterozygous mutation of the *CDAN1*-gene.

Case report

The propositus (AN.TC., DOB 08.04.2007, CDA-UPN 499/01 of the German Registry on Congenital Dyserythropoietic Anemias), is the only son of a non-consanguineous Chinese mandarin couple. Both parents are healthy with normal blood counts. The neonate was icteric and pale, but otherwise normal. Blood counts showed severe anemia with a hemoglobin concentration of 7.1 g/dl. No blood transfusions were given, and at the age of 2 months, the infant was first seen at the Institute of Hematology & Blood Diseases Hospital in Tianjin, China. He was pale and slightly icteric with normal weight (5.1 kg) and length (55 cm). Syndactyly was noted at the left foot, and x-rays showed syndactyly of the 4th and 5th metatarsal. Relevant laboratory data are shown in Table 1. Red cell enzyme concentrations as well as osmotic hemolysis were within normal limits, excluding the most common types of hereditary hemolytic anemias. The inadequate increase of reticulocytes in the presence of severe anemia suggested the diagnosis of a CDA, and bone marrow aspiration was performed at the age of 10 weeks.

The peripheral blood smear showed grade 2 anisopoikilocytosis, with some basophilic stippled erythrocytes and 9% mature erythroblasts. In the bone marrow, cellularity was increased due to marked erythropoietic hyperplasia, with an E:G ratio of 3.2:1 (normal reference 0.2 to 0.8). More than 30% of the more mature erythroblasts showed the well known aberrations seen in CDA I, with various abnormalities of chromatin structure and internuclear bridges (Fig. 1). Transmission electron microscopy showed typical aberrations of the chromatin structure in more than 80% erythroblasts with Swiss-cheese-like structure of the heterochromatin and widening of the pores of the perinuclear membrane [6, 23].(Figure 2).

Table 1 Results of laboratory examinations

WBC	5.3×10^9/l	Plasma Hb	24.7 mg/l (0–50)
RBC	2.0×10^{12}/l	Haptoglobin	18g/dl (50–200)
PCV	0.19	G6PD activity	Normal
Hb	5.8 g/dl	PK activity	Normal
MCV	94 fl	P5′-NT	3.45 (2.6–3.52)
MCHC	31 g/dl	$AGLT_{50}$	290 s (> 1,800)
MCH	29 pg	HBF %	0.124 (0–0.025)
NRBC	9%	HBA2%	0.026 (0–0.035)
RETIC	4.3%	Osmotic fragility	Normal

Hb Hemoglobin, *PVC* packed cell volume, *MCV* mean corpuscular volume, *MCHC* mean corpuscular hemoglobin concentration, *MCH* mean corpuscular hemoglobin, *NRBC* nucleated red blood cells, *G6PD* glucose-6-phosphate dehydrogenase, *P5′-NT* pyrimidine 5′-nucleotidase test, *AGLT* acidified glycerol lysis time

Molecular genetics

Genomic DNA was isolated from peripheral blood cells of the propositus and both parents with the QIAmp DNA Blood Mini Kit (QIAGEN) according to the manufacturer's instructions. As described previously, coding sequences and the exon/intron boundaries of the *CDAN1*-gene were amplified using the Taq polymerase system (QIAGEN). PCR products were sequenced directly using the BigDye Terminator v1.1 Cycle Sequencing Kit and an ABI 3100 Sequencer. The propositus showed two different mutations in exon 14 of *CDAN1*, namely Val 690 Ala (maternal allele) and Arg 714 Trp (paternal allele; amino acids are numbered according to Genbank accession no. NP_612486). Thus, the child is a compound heterozygote for a mutated *CDAN1*-gene.

Phenotype and genotype are similar to patients with CDA I from Israel and from Europe.

Discussion

The family described in this article is the first case reported from China. Mutations in exon 14, as observed in the present family, were more frequent than others in the French and German series [2, 9]. Arg 714 Trp has been previously detected in a German family, but Val 690 Ala was not yet published. The functional consequences of these missense mutations are presently unknown due to a lack of knowledge of codanin function. Severe anemia with the need of red cell transfusions in CDA I neonates and infants is common [2, 17]; but in the majority of cases, regular transfusions are not needed in young adults [9, 18]. Iron overloading by red cell transfusions and/or up regulation of enteral iron resorption is a regular consequence of ineffective erythropoiesis in individuals with CDA I, with significant morbidity and mortality if not properly controlled. Treatment with interferon α, first found to relieve the anemia and to normalize the enteral iron absorption in young adults [13], is well tolerated and effective also in young infants [2, 14], and therefore an early diagnosis of this very rare type of hereditary disorder should be sought in neonates and infants with unexplained chronic anemia, especially when associated with neonatal

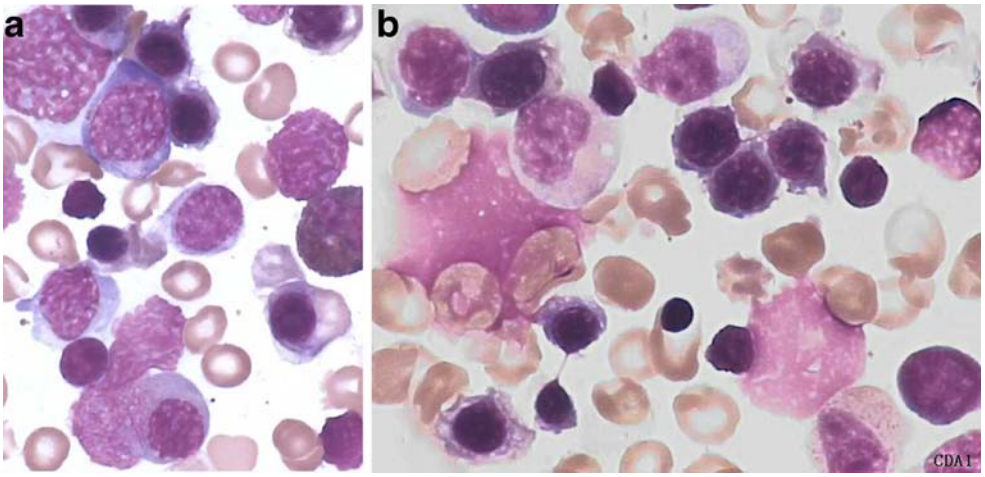

Fig. 1 **a**, **b** Bone marrow smear showing erythroblasts with abnormal chromatin structure and internuclear bridges

manifestations, jaundice, splenomegaly, and with absent or inadequate reticulocytosis.

Single cases of CDA I were reported from India and Japan, but sufficient data including electron microscopy is only available from five reports [4, 10–12]. Most probably, many cases remain undiagnosed, possibly when they live in regions where specialized diagnostics are not available for the majority of residents. At present, there are no data that permit any considerations whether or not gene mutant frequency in others regions of the world is lower than in Europe.

CDA I, as well as the more frequent type CDA II (HEMPAS) can be easily recognized by evidence of its congenital and/or hereditary nature, laboratory signs suggesting ineffective erythropoiesis and, particularly, the highly specific morphological aberrations of the erythroblasts. Nevertheless, many cases remain undiagnosed for many years, and in some patients, the correct diagnosis is made not before iron overloading with potential organ damage had occurred [9]. The morphological changes, as shown in Fig. 1, are more easily recognized by electron microscopy (Fig. 2). Mutations at the *CDAN1*-gene are specific for CDA I in patients with the phenotype as described; there are, however single families without mutations [9, 20], most probably suggesting a different mutated gene resulting in a similar phenotype [1]. Skeletal dysmorphologies, particularly metatarsal syndactyly as present in the patient described, are seen in about 20% of all CDA I patients [5]; they are, however, in no way specific for this special entity of the congenital bone marrow failure syndromes.

This report may increase the alertness of pediatricians and hematologists to identify patients with CDA I in China and other Asian countries.

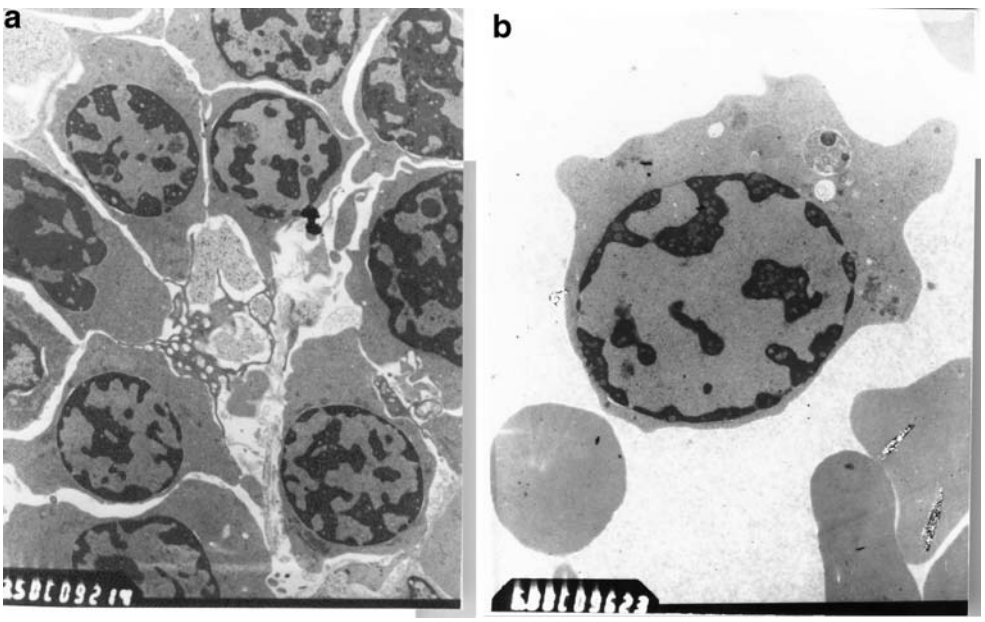

Fig. 2 Electron micrograph showing erythroblasts with widened nuclear pores (*arrow*) and typical Swiss-cheese-like nucleus in erythroblastic islands, **a** original magnification ×3500; **b** ×2500. Processing as previously described [16]

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