Frequency of congenital dyserythropoietic anemias in Europe

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Abstract

Congenital dyserythropoietic anemias (CDAs) are rare hereditary disorders characterized by ineffective erythropoiesis and striking abnormalities of erythroblast morphology. The mutated genes are known for the most frequent types, CDA I and II, but data about their frequency do not exist. The objective of this retrospective study was to estimate the frequency of CDA I and II, based on all cases reported in the last 42 yr in publications and identified registries or surveys. Reports were collected of 124 and 377 confirmed cases of CDA I and CDA II cases, respectively. The cumulated incidence of both types combined varied widely between European regions, with minimal values of 0.08 cases/million in Scandinavia and 2.60 cases/million in Italy. CDA II is more frequent than CDA I, with an overall ratio of approximately 3.2, but the ratio also varied between different regions. The most likely explanations for the differences are both differences in the availability of advanced diagnostic procedures and different levels of the awareness for the diagnosis of the CDAs. The estimations reported here are most probably below the true incidence rates, because of failure to make the correct diagnosis and to underreporting. Limited data do not suggest differing levels of risk in identified ethnic groups.

Key words congenital dyserythropoietic anemia; frequency; epidemiology; rare diseases

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Deceased.

This work is dedicated to our late friend, Professor Sunitha Wickramasinghe.

Supported by the University of Ulm, the Else Kröner-Fresenius Stiftung Bad Homburg, Germany and the European Network on Rare Congenital Anemias (ENERCA).

Accepted for publication 25 February 2010 doi:10.1111/j.1600-0609.2010.01440.x

Congenital dyserythropoietic anemia (CDA) was first described in 1967. Soon after the first reports, it became evident that different types exist (1), which share ineffective erythropoiesis as the main mechanism of the anemia and which are all characterized by morphological abnormalities of the erythroblasts, but which are of distinct phenotype and genotype. Specific diagnostic data were first reported from indigenous populations and from
immigrant ethnic groups living in Europe and later from other regions of the world. The CDA s are rare (2), but exact incidence data do not exist. From preliminary data obtained from case reports or data collated in registries and surveys in Germany, Italy, France, and the UK, CDA II and CDA I, in that order, seem to be the least uncommon types. For both types, there are well-accepted phenotypic criteria (3, 4). They are inherited following an autosomal recessive pattern. In the vast majority of genotyped CDA I, mutations of the CDAN1-gene (4–6) were found, while all cases of CDA II were associated with SEC23B mutations (7, 8).

Most cases of CDA III come from two large families where inheritance follows an autosomal dominant pattern. The presence of so-called sporadic cases suspected to have a recessive inheritance is controversial. Aberrant or variant types have been described in single families, and the phenotypic definition is still preliminary (2, 9, 10).

Here, we report of an estimate of the frequency of CDA I and CDA II in Europe.

Patients and methods

Source of data

The study covered data from all member states of the European Union, Norway, and Switzerland. Residency was defined as country of domicile at the time of diagnosis. The following sources were used to identify cases of CDA.

1. Publications: All publications describing cases of CDA were systematically collected by H.H. since the first description of CDA in 1967. Completeness was checked by review of online databases (National Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed) for key words ‘congenital dyserythropoietic anemia’ or ‘cda’, most recently on 1 August 2009. All reports were analyzed for citations of previous case reports. In addition, early reports were retrieved from three monographs (11–13). To identify the individuals reported in publications, the authors were asked for additional identifying data (see below) by correspondence.

2. Registry data: The German registry on CDAs at Ulm collects cases of all types of CDA, and the International registry at Naples in Italy all cases of CDA II. These registries initially aimed through surveys to recruit all cases from the German-speaking countries (Germany, Austria, and Switzerland) and from Italy, respectively. Repeated requests to notify patients with CDA were distributed to all members by the national hematological societies of the German-speaking countries. For Italy, the CDA registry was compiled after getting in touch with all hematological centers and it is reasonable that all hematologists have been reached. CDAII cases diagnosed in Milan were identified by SDS–PAGE studies in cases referred for suspected for congenital membrane defect, mainly suspected to have hereditary spherocytosis. When the expertise of these centers became known through their publications, they received requests from many other countries for diagnostic confirmation of suspected cases or advice on management of patients with CDA. Other cases were collected in the same way by diagnostic centers in other European countries. These included the Department of Pediatrics and the French Center for Inherited Erythocyte and Erythropoiesis Disorders at Hopital Bicetre (France) (J.D; B.B, L.G.), the Laboratory of the late S. Wickramasinghe at Imperial College, London (UK), the Hematology Center at the Fundeni Hospital in Bucharest collecting cases from Romania (A.C.), and the Oxford CDA Research Initiative in Oxford (UK) (R.R).

3. Further data collection: F. Gilsanz and J. A. Munoz collected unpublished cases from Spain, M. Ahmed from the UK, and G. G. Smolenska-Sym from Poland.

4. Demographic data: Country data on population number were obtained from the United Nations Demographic Yearbook (UNDYB) 2008.

5. Consanguinity data were obtained from Bittles (14) and http://www.consang.net.

6. Frequency of heterozygotes was calculated using the Hardy–Weinberg equation.

Diagnostic criteria

Diagnostic criteria were used as defined in previous reports (3, 4). More recently, mutations of the CDAN1 and the SEC23B genes were accepted as confirmatory tests for CDA I and CDA II, respectively. In the cases extracted from the literature, we accepted their diagnosis made after diligent analysis of the details described.

Data management and identification of cases and families

All data collected as described were coded according to the system used in the database of the German Registry on CDAs, Ulm, Germany. Any individual was pseudonymized using a code (three digits for family/two digits for family member), which does not allow identification of personal data. Use of such data for scientific research was approved by the ethical committee of the University of Ulm (222/2003).

Multiple publications of identical cases and multiple notifications in more than one registry or survey are serious methodological problems in very rare disorders such as CDA. We took the utmost care to detect double or
multiple notifications. The reports from the registries mentioned above and all papers containing patient data from the same institution or with identity of at least one author were cross referenced. When identity of described cases was suspected, we tried to obtain further information by correspondence.

Lists of cases in MS-Word or MS-Excel format were provided from registries or referral centers by the responsible scientists, who are all authors of this work. The types of data provided were not uniform and dependent on the national rules for data protection.

First-order attributes were CDA type, sex, date of birth (DOB), date of first diagnosis of CDA, country of residence at this date, and date of last contact or date of death. Full names or initials were used as controls to detect possible errors in DOBs. Definition of data of ethnicity was not uniform. For individuals or families who immigrated many years ago, and often acquired the citizenship of the country of residence, the country of birth of the grandparents was used. Other means of identifying ethnicity were the ongoing command of the language of the country of origin or national forenames or surnames, which prompted a special interview with the propositus or members of his/her family.

Any single case was also recorded as a family and any family with more than one case included first- and second-degree relatives of the propositus.

Data on parent’s consanguinity were obtained from interviews with patients and their families; pedigrees were constructed from this information by CYRILLIC version 2.1.3 (Cherwell scientific publishing Ltd.).

The study period for determination of cumulative incidence was considered to be the last 42 yr, and numerical estimation was given in cases /million inhabitants.

Results

On the index date of 01.08.2009, we have recorded 169 cases from 143 families with CDA I, and 454 cases from 356 families with CDA II worldwide. The number of cases in Europe expressed as a 42 yr cumulative incidence of a very rare disease is shown in Fig. 1. Of the total of 489 cases, 15% had been published before they were notified in any registry or referral center. However, among cases from countries without registries or referral centers, data were derived from published case reports in 55% and only 45% from notifications to these centers, mainly submitted for confirmation of the suspected diagnosis or consultations sought for management of these patients.

The total number of cases and families in Europe is shown in detail in Table 1. To make the information manageable in spite of the small numbers of cases reported from most countries, we have aggregated regions with high fluctuations between the countries shown in Fig. 1. The distribution confirms previous observations showing that CDA II is more frequent than CDA I, with an overall ratio of approximately 3.0. The ratio is highest in Italy and lowest in the UK ($P < 0.0001$; chi-square test for homogeneity among the countries with number of cases $\geq 20$, based on the families as statistical units). The fact that the Italian registry in Naples is largely confined to CDA II and the referral center in Milan has special interest in red cell membranopathies such as hereditary spherocytosis whereas the interest of the British centers concentrate on CDA I suggests that this is because of a bias of notification rather than because of the true frequency of either type in different geographic regions. Differences in sex ratios are insignificant. The average number of affected members of any family in both types is nearly identical with 1.16 and 1.12. Cumulative incidence of CDA I and II varies
widely between the aggregated regions (Table 2). If only the aggregated regions with more than 40 notified cases are compared, the magnitude of frequency of both types combined is 1–2 families ⁄ million inhabitants.

The age at which the diagnosis was made is shown in Fig. 2. Both types of CDA were first described in adults. We expected that the proportion of cases recognized in infancy or childhood would be greater after 1990, when pediatric hematologists became familiar with the novel disease entity. Comparison of Fig. 2a and b verified this hypothesis. However, even after 1990, the correct diagnosis of these inborn disorders is still delayed in many cases. Hemolytic anemia, particularly hereditary spherocytosis, was the most frequent erroneous diagnosis before the correct diagnosis was made.

Complete data on ethnic origin of families with CDA of any type when compared to the fractions of indigenous to immigrant populations are available from the German registry for families residing in the German-speaking countries. Although the respective numbers are small, there is no evidence of higher incidence in any of the immigrant groups when compared the indigenous population (Fig. 3). Similar data were seen in the referral center in Milan (data not shown).

### Discussion

This is the first report on the frequency of the CDAs, a group of very rare congenital diseases. Epidemiological information is of interest for further research and for better diagnosis, management of affected individuals and for genetic counseling. The reports of the German Registry on CDAs (3, 4) and case reports from the literature (15–20) show that iron overload with organ damage is a serious complication of these conditions with a disproportionate contribution to associated mortality and morbidity. This is more of an issue when there is a delay in diagnosis either because of poor recognition or because of limited diagnostic capabilities as is often the case.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>CDAI</th>
<th></th>
<th>CDA II</th>
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<td>Cases</td>
<td>Ratio CDA II/I</td>
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<td>26</td>
<td>1.60</td>
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<td>–</td>
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<td>17</td>
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<td>5</td>
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<td>–</td>
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<tr>
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<td>–</td>
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<tr>
<td>Ireland/Great Britain</td>
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<td>36</td>
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<td>1.90</td>
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<tr>
<td>Poland</td>
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<td>1</td>
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<td>122</td>
<td>1.03</td>
<td>0.90</td>
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The study was limited to CDAs type I and type II for several reasons. First, accepted definitions for diagnosis are available only for these two major types. We critically reviewed the clinical and laboratory data of every patient included, and erroneous diagnoses are unlikely. Second, the group of so-called variants of CDA is very heterogeneous; in some case reports, the data are not sufficient to exclude another congenital anemia with similar phenotype. Third, the number of CDA variants with similar phenotype is very small, mostly confined a few families. This is also true for families with CDA III other than the two large families with autosomal dominant inheritance.

Incidence rates are usually expressed as the number of newly detected events per annum and population number of the geographic region studied. Here, we report the cumulative incidence (synonym to incidence proportion), which determines the number of cases collected over a period of time. The time interval between the first descriptions in 1967 and the index day was 42 yr. Because death dates were not available for all cases collected apparent prevalence could not be calculated from these data. Median life expectancy is more than 70 yr in the patients who are resident in Germany, Austria, and Switzerland (data not shown), and therefore the data presented are close to the lifetime prevalence. In contrast to thalassemia and sickle cell disease (21), there is no available neonatal screening for the CDAs. Therefore, the numbers of estimated annual affected conceptions, a parameter frequently used to express the frequency of hereditary disorders (21), cannot be directly assessed. Because of almost absent mortality in early life, it should be approximately equivalent to the numbers of families with at least one affected child.

The data on frequency show large variations, with an average of approximately one case per million inhabitants ($P = 0.0002$ for CDA I and $P < 0.0001$ for CDA II, chi square-goodness-of-fit-test to the population size for the countries with number of cases $\geq$20, based on the families as statistical units). Italy shows a much higher incidence as compared to all other regions with more than 2.49 cases /million notified, exclusively because of the large number of cases with CDA II, particularly from South Italy (22). If genetic reasons are excluded, an explanation for the high number of cases of CDAII in Italy could be that the two reference centers (one in North and one in South Italy) routinely perform sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) analysis in all cases referred for suspected hemolytic anemia. Altogether, the most likely hypothesis to explain the differences between the aggregated regions seen from Table 2 are both differences of advanced diagnostic procedures available for all citizens and the awareness for the diagnosis of CDA. Indirect evidence supporting the latter hypothesis is the very high ratio of CDA II to CDAI reported from Italy and the low ratio from the UK, which correlates with the presence of registries and referral centers largely confined to either type.

True frequency of CDA I and CDA II is most probably higher than estimated in this study. The number of cases as shown in Fig. 1 and consecutively the population-based cumulated incidence calculated in Table 2 are minimal values. For CDA II, the figures from Italy are most probably closer to the true incidence than the figures from most other countries and are strong evidence of substantial underestimation of cases in other regions. The observation that in this congenital disease, the correct diagnosis is often delayed up to adulthood (Fig. 2)
suggests that even today many cases have an erroneous
diagnosis or, in cases with moderate of only borderline
anemia, remain undetected. In addition, one has to
assume that not all cases where the correct diagnosis was
made were notified to one of the registries or referral
centers, and were not published as case reports. The low
population-based frequency in some European regions
estimated for the first time in this report will hopefully
prompt increased awareness for the CDA and broader
use of methods for appropriate diagnosis in cases of
unclassified or misclassified congenital anemias.

The data on possible ethnic groups at risk are to be
regarded with care, because the numbers available are
small. Data from Germany shown in Fig. 3 correspond
to families that immigrated from Bolivia and Rumania
in Italy (data not shown). However, they suggest that in
contrast to the thalassemias and the sickle-cell diseases,
no differences exist. This is supported by the fact that
families with CDAs have been reported from many
countries outside Europe. As in other hereditary disor-
ders with autosomal recessive inheritance, the degree of
consanguinity based on cultural traditions (14) may influ-
ence their prevalence.

Acknowledgements

The authors thank all physicians and scientists from
many European countries who contributed data and
bone marrow specimens.

References

1. Heimpel H, Wendt F. Congenital dyserythropoietic ane-
emia with karyorrhexis and multinuclearity of erythro-
2. Heimpel H, Iolascon A. Congenital dyserythropoietic ane-
emia. In: Beaumont C, Beris Ph, Beuzard Y, Brugnara C
eds. Disorders of homeostasis, erythrocytes, erythropoiesis,
2 edn. Paris: European School of Haematology; 2009:
178–201.
dyserythropoietic anemia type II: epidemiology, clinical
appearance, and prognosis based on long-term observa-
dyserythropoietic anemia type I (CDA I): molecular genet-
ics, clinical appearance and prognosis based on long-term
5. Dgany O, Avidan N, Delaunay J, et al. Congenital dys-
erthropoietic anemia type I is caused by mutations in
ular variability in congenital dyserythropoietic anemia

W, Iurlo A, Marcello AP, Righetti PG, Zanella A. Con-
genital dyserythropoietic anemia type II (CDAII) is
caused by mutations in the SEC23B gene. Hum Mutat
affecting the secretory COPII coat component SEC23B
cause congenital dyserythropoietic anemia type II. Nat
9. Wickramasinghe SN. Congenital dyserythropoietic anae-
mas: clinical features, haematological morphology and
10. Wickramasinghe SN, Wood WG. Advances in the under-
standing of the congenital dyserythropoietic anemias. Br
11. Lewis SM, Verwilghen RL. Dyserythropoiesis. London:
12. Porter R, Fitzsimons DW. Congenital disorders of erythro-
13. Sansone G. Le Anemie diserythropoietiche congenite. Pisa:
14. Bittles AH. Consanguinity and its relevance to clinical
15. Bird AR, Jacobs P, Moores P. Congenital dyserythropoi-
etic anaea (type II) presenting with haemosiderosis. Acta
loading in congenital dyserythropoietic anaemias and
congenital sideroblastic anaemias. Br J Haematol
17. Greiner TC, Burns CP, Dick FR, Henry KM, Mahmood
I. Congenital dyserythropoietic anemia type II diagnosed
in a 69-year-old patient with iron overload. Am J Clin
18. Halpern Z, Rahmani R, Levo Y. Severe hemochromatosis:
the predominant clinical manifestation of congenital dys-
180.
19. Hovinga JA, Solenthaler M, Dufour JF. Congenital dys-
erthropoietic anemia type II (HEMPAS) and haemo-
chromatosis: a report of two cases. Eur J Gastroenterol
20. Schatanek W, Hufnagl HD, Meiser RJ, Berberich R.
Kongenitale dyserythropoetische Anämie mit Eisenspe-
erchenerkrankheit. Munch Med Wochenschr 1972;114:1933–
1936.
haemoglobin disorders in Europe: an overview. Scand
22. Iolascon A, Servedio V, Carbone R, Totaro A, Carella M,
Perrotta S, Wickramasinghe SN, Delaunay J, Heimpel H,
Gasparini P. Geographic distribution of CDA-II: did a
founder effect operate in Southern Italy? Haematologica