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Acute leukaemia in children with Down syndrome: a population-based Nordic study

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Summary

To determine the epidemiology and outcome of children with Down syndrome (DS) diagnosed with acute leukaemia in the Nordic countries, data registered in the Nordic Society of Paediatric Haematology and Oncology (NOPHO) population-based leukaemia registry were analysed. Of 3494 children with acute leukaemia diagnosed between July 1984 and December 2001, 136 patients (3·9%) with DS were identified. 2·1% of the children with acute lymphoid leukaemia (ALL) and 14·0% of the children with acute myeloid leukaemia (AML) had DS. In ALL, DS patients had similar age and sex distribution and no major differences in blood counts compared with non-DS children. None of the DS patients had T cell leukaemia. Outcome was inferior to that of non-DS children and treatment results did not improve over time. In AML, DS patients showed a significant female predominance and all but one were <5 years old. DS patients with AML had significantly lower platelet and white blood cell counts and two-thirds were type M7 as according to the French–American–British classification. None of the patients <5 years of age had typical AML cytogenetic aberrations. Outcome was far better in the DS group. DS patients treated for AML after 1992 had an excellent outcome (probability of event-free survival, 83 ± 6%). The high proportion of female DS patients with AML is unexplained. The differing treatment results in AML *versus* ALL need further evaluation and represent a challenge for the coming years.

Keywords: acute lymphoid leukaemia, acute myeloid leukaemia, Down syndrome, children, epidemiology.

The increased incidence of leukaemia in individuals with Down syndrome (DS) was observed nearly 50 years ago (Krivit & Good, 1957). Since then, many reports have confirmed the association and described the special features of the leukaemias seen in DS children (Robison *et al*, 1984; Levitt *et al*, 1990; Ravindranath *et al*, 1992; Zipursky *et al*, 1992; Slordahl *et al*, 1993; Creutzig *et al*, 1996; Lie *et al*, 1996; Dördelmann *et al*, 1998; Lange *et al*, 1998; Chessells *et al*, 2001; Hasle, 2001; Goldacre *et al*, 2004). The relative risk of acute leukaemia in the first 5 years of life is 56 times that of non-DS individuals (Hasle *et al*, 2000), and acute myeloid leukaemia (AML) is equally frequent as acute lymphoid leukaemia (ALL) (Lange, 2000). AML in DS children is characterized by unique features. According to the proposals for a paediatric approach to the World Health Organization classification of myelodysplastic and myeloproliferative diseases, it should be classified as a separate disease entity, 'Myeloid leukaemia of Down Syndrome' (ML-DS) (Hasle *et al*, 2003).

The majority of studies concerning DS and leukaemia are based on institutional reports. Earlier studies often did not include all of the DS patients, but they have been enrolled more consistently in recent studies. Only a few studies have been performed in a population-based setting (Craze *et al*, 1999; Stiller & Eatock, 1999; Hasle *et al*, 2000).

In the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) a common registry for children with ALL was established in 1981 and for AML in 1984 by the Nordic Society for Paediatric Haematology and Oncology

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(NOPHO). Information on all cases of childhood acute leukaemia in the Nordic population of 23 million inhabitants is registered, thus representing a unique possibility to perform population-based studies.

During the years 1984–2001 a total of 136 children with DS were registered in our ALL and AML registry. We present here the epidemiological and clinical features, as well as the therapy results, of these patients.

Patients and methods

All children aged less than 15 years with *de novo* AML or non-B ALL registered in the common Nordic leukaemia registry between July 1984 and December 2001 were included. The data were collected in a uniform way across disease types and countries. Patients with secondary leukaemia and congenital transient abnormal myelopoiesis were excluded. After exclusion, 3494 children remained for analysis. Clinical and epidemiological data as registered in the central database were analysed. Eighteen patients with AML (eight non-DS, 10 DS, all died) did not receive therapy and are excluded from analysis of outcome. All non-treated DS patients were from the early period 1984–92, and five had complex congenital heart disease. The decision not to treat was made by the attending physician in accordance with the parents. Two DS patients with ALL (DS ALL), both with congenital heart disease, died on day 15 and 16 from diagnosis respectively. It is uncertain if these children received leukaemia-directed therapy. They were classified as treated children.

Diagnosis

The diagnosis of AML/ALL was based on the presence of more than 25% blasts in the bone marrow and typical findings of blood and bone marrow histochemistry, immunophenotyping, and cytogenetic analysis if available. The diagnosis was made at the local centres without central review.

French–American–British (FAB) classification of AML

During the period from 1984 to 1992 the classification of AML was under continuous improvement. Thus, results of the FAB classification were incomplete and not fully reliable; in particular, the M7 leukaemias (acute megakaryocytic leukaemia, AMKL) were under-diagnosed. FAB types are therefore presented for the last trial (NOPHO-AML 93) only.

Cytogenetics

Cytogenetic analysis was not available in all centres during the early study period. Consequently, the analysis of cytogenetic results was performed for the period after 1986 (ALL) and 1992 (AML). Cytogenetics were performed by chromosome banding analyses of bone marrow and/or peripheral blood samples using standard methods in 15 cytogenetic laboratories in the Nordic countries. The definition and description of clonal abnormalities followed the recommendations of the International System for Human Cytogenetic Nomenclature (Mitelman, 1995). Specific analyses [fluorescence *in situ* hybridization (FISH), Southern blot, and reverse-transcription polymerase chain reaction] have been increasingly used during the study period, to characterize more precisely the chromosomal abnormalities found as well as to detect *MLL* rearrangements. One example is the t(12;21) (TEL;AML1) in the ALL cohort. However, the results are not included in this report because the small number of tested DS patients precluded meaningful analyses.

Therapy

The ALL treatment and risk group stratification has been described previously in detail (Gustafsson *et al*, 1998, 2000). For the first 2 years, the five countries used regional and national protocols. From 1986 standard and intermediate risk patients received uniform treatment, whereas high-risk patients were still treated according to national protocols. In 1992, the first common Nordic treatment protocol (NOPHO-ALL 92) was introduced for all risk groups. None of the protocols contained treatment modifications for DS patients.

The AML treatment consisted of three consecutive Nordic protocols (NOPHO-AML84, NOPHO-AML88 and NOPHO-AML93). The protocols have been described previously (Lie *et al*, 1996, 2003). None of the protocols contained specific recommendations for the treatment of DS patients. Dose reductions were made according to the judgement of the local oncologist. The NOPHO 88 and 93 protocols recommended bone marrow transplantation in first remission if a human leucocyte antigen (HLA)-identical sibling was available. However, based on the good treatment results of chemotherapy alone in DS patients together with a higher risk of toxic complications, transplantation has not been used in DS patients.

Statistical methods

Data were analysed as of January 2004. The Statistical Package for the Social Sciences (SPSS) Analysis System Version 12·0 was used in the statistical analysis. Event-free survival (EFS) was calculated from date of diagnosis to date of the first negative event (induction failure, death in remission, relapse, secondary malign neoplasm) or to last follow-up for children in continuous complete remission (CCR); overall survival (OS) was calculated from date of diagnosis to date of death, or date of last follow-up for children alive. Patients not achieving complete remission were considered failures at time zero. The probability of EFS (p-EFS) and OS (p-OS) was calculated using the Kaplan–Meier method and significant differences between subgroups were compared using the Log Rank test. Proportions have been compared by chi-square tests.

Results

Of the 3494 children with acute leukaemia available for analysis, 136 had DS (3·9%). The distribution of the patients was as follows: non-DS ALL: 2915, DS ALL 64 (2·1% of all ALL cases), non-DS AML 443, ML-DS 72 (14·0% of AML). The proportion of DS patients did not differ significantly between the five countries.

ALL

The age distribution of DS and non-DS patients was quite similar (Table I; Fig 1), but the DS group contained no infants and had a more distinct peak at the age of 2 years (borderline significant, $P = 0{\cdot}06$). The youngest DS patient was 14 months at diagnosis. The sex ratio showed no difference between non-DS and DS patients.

The median platelet count at diagnosis was significantly lower in DS patients. There were no significant differences in haemoglobin levels and white blood cell counts (WBC). However, there was a tendency towards a lower proportion of high and very high WBC in the DS group.

The risk stratification according to the NOPHO protocol (Gustafsson *et al*, 2000) revealed no major differences between DS and non-DS children. Immunophenotyping showed a complete absence of T cell leukaemia in DS patients. There were no differences concerning central nervous system involvement and presence of mediastinal mass.

Cytogenetic results were obtained in 48 patients with DS. Of these, 21 had a normal karyotype and 27 showed cytogenetic aberrations. DS patients had a significantly lower frequency of hyperdiploidy. The most common changes in the modal number were gain of chromosome X, 14, 17 and 21. Investigation by chromosome banding analyses did not reveal any of the structural aberrations commonly found in non-DS ALL, such as t(9;22) or t(1;19). Two patients showed a t(8;14)(q11;q32).

Treatment results are shown in Table II and Fig 2A, B. DS children did worse than the non-DS children. This was mainly due to a higher induction failure rate (14·1% vs. 1·8%). Comparing the two treatment periods 1984–92 vs. 1993–2001, there was a significant prognostic improvement during the second period in the non-DS group (p-EFS 67 ± 1 vs. 73 ± 1, $P < 0{\cdot}01$). In contrast, the DS group showed a slight, non-significant decrease in p-EFS in the second treatment period (57 ± 9 vs. 40 ± 13; $P = 0{\cdot}5$). The DS group showed a trend towards increasing induction failure rate but lower relapse rate over time.

AML

A high proportion of the non-DS patients were aged 0 or 1 year (28·4%). Above this age there was a relatively flat distribution. The DS group comprised few infants (4·2%) and all but one were younger than 5 years old (Table III; Fig 3).

Table I. ALL: non-Down syndrome *versus* Down syndrome (DS).

	Non-DS	DS
Total	2915	64
Gender		
Female	1356 (46·5)	29 (45·3)
Male	1559 (53·5)	35 (54·7)
Age (years)		
<1	87 (3·0)	0 (0)
1–<5	1575 (54·0)	37 (57·8)
5–<10	786 (27·0)	15 (23·4)
≥10	467 (16·0)	12 (18·8)
Median	4	4
WBC count ($\times 10^9$/l)		
<10	1460 (50·1)	34 (53·1)
10–<50	882 (30·3)	22 (34·4)
50–<100	250 (8·6)	4 (6·3)
≥100	315 (10·8)	4 (6·3)
Missing	8 (0·3)	–
Median WBC	10·0	9·8
Maximum WBC	1400·0	540·0
Platelet count ($\times 10^9$/l)		
<50	1423 (48·8)	37 (57·8)
≥50	1434 (49·2)	25 (39·1)
Missing	58 (2·0)	2 (3·1)
Median	50	38*
Hb (g/dl)		
<10	2365 (81·1)	48 (75·0)
≥10	507 (17·4)	15 (23·4)
Missing	43 (1·5)	1 (1·6)
Median	75	78
Risk group (non-B-cell)		
Infant	87 (3·0)	0 (0)
Non-high risk	2019 (69·3)	48 (75·0)
High risk	809 (27·8)	16 (25·0)
Immunophenotype		
B-precursor	2562 (87·9)	59 (92·2)
T cell	265 (9·1)	0 (0)*
Missing/others	66/22 (3·1)	3/2 (7·8)
Mediastinal mass present	214 (7·3)	4 (6·3)
CNS leukaemia present	87 (3·0)	2 (3·1)
Cytogenetics		
Result obtained	1923 (66·0)	48 (75)
Normal karyotype	723 (37·6)	21 (43·8)
Clonal aberrations	1200 (62·4)	27 (56·2)
>50 Chromosomes	570 (29·6)	2 (4·2)***

Results are in number (%).
Significant with *$P < 0{\cdot}05$; **$P < 0{\cdot}01$; ***$P < 0{\cdot}001$ (chi-square test).
CNS, central nervous system.

The youngest DS patient was 8 months at diagnosis. The sex distribution was equal in the non-DS cohort, whereas the DS children had a strong female predominance (ratio female:male 2·27 vs. 1·06 in non-DS patients).

Children with DS had significantly lower WBC at diagnosis. None had a count higher than 100×10^9/l, compared with 14·7% in the non-DS group. A significantly higher proportion

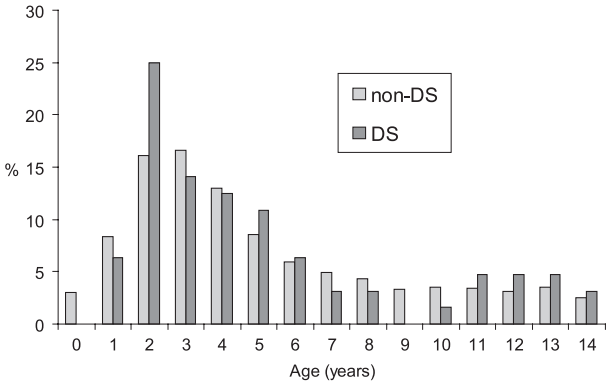

Fig 1. Age distribution (as a percentage) in 2979 patients with ALL without Down syndrome ($n = 2915$) and with Down syndrome ($n = 64$).

Table II. Treatment results.

	Non-DS ALL	DS ALL	Non-DS AML	ML-DS
Total	2915	64	435	62
Induction failure	50 (1·7)	9* (14·1)	57 (13·1)	10† (16·1)
Relapse (in CR 1)	722 (24·8)	17 (26·6)	177 (40·7)	7 (11·3)
Deaths (in CR 1)	62 (2·1)	2 (3·1)	18 (4·1)	1 (1·6)
Total events	834	28	252	18
Alive in CR 1	2081 (71·4)	36 (56·3)	183 (42·1)	44 (70·9)
p-EFS (at 5 years)	73 ± 1	59 ± 7	43 ± 2	71 ± 6
p-EFS (at 10 years)	70 ± 1	51 ± 7	42 ± 2	71 ± 6
p-OS (at 5 years)	84 ± 1	65 ± 7	54 ± 2	74 ± 6
p-OS (at 10 years)	80 ± 1	57 ± 7	53 ± 2	74 ± 6
Period 1 (1984–92)	1340	28	205	24
p-EFS (at 5 years)	69 ± 1	64 ± 9	35 ± 3	54 ± 10
p-EFS (at 10 years)	67 ± 1	57 ± 9	34 ± 3	54 ± 10
Induction failure	32 (2·4)	3 (10·7)	37 (18·0)	8 (33·3)
Relapse (in CR 1)	397 (29·6)	8 (28·6)	86 (42·0)	3 (12·5)
Deaths (in CR 1)	28 (2·1)	1 (3·6)	13 (6·3)	1 (4·2)
Period 2 (1993–2001)	1575	36	230	38
p-EFS (at 5 years)	76 ± 1	54 ± 9	50 ± 3	83 ± 6
p-EFS (at 10 years)	73 ± 1	40 ± 13	49 ± 3	83 ± 6
Induction failure	18 (1·1)	6 (16·6)	20 (8·7)	2 (5·3)
Relapse (in CR 1)	325 (20·6)	9 (25·0)	91 (39·6)	4 (10·5)
Deaths (in CR 1)	34 (2·1)	1 (2·8)	5 (2·2)	0 (0)

Eighteen patients (eight non-DS AML, 10 ML-DS, all from the first period 1984–92) did not receive therapy and were excluded from outcome analysis.

Results are given as a percentage (%) with SE for pEFS and p-OS, otherwise results are number (%).

p-EFS: probability of event-free survival, p-OS: probability of overall survival, CR 1: first complete remission.

*Resistant disease 0, infection/aplasia 9; †Resistant disease 4, infection/aplasia 6.

presented with platelet counts $<50 \times 10^9$/l. No differences were found regarding the haemoglobin value.

FAB subtypes are shown for the second period from 1993 to 2001 (Table III). Two-thirds of the DS patients were classified as M7, in contrast to 6·4% in the non-DS group. This difference was highly significant.

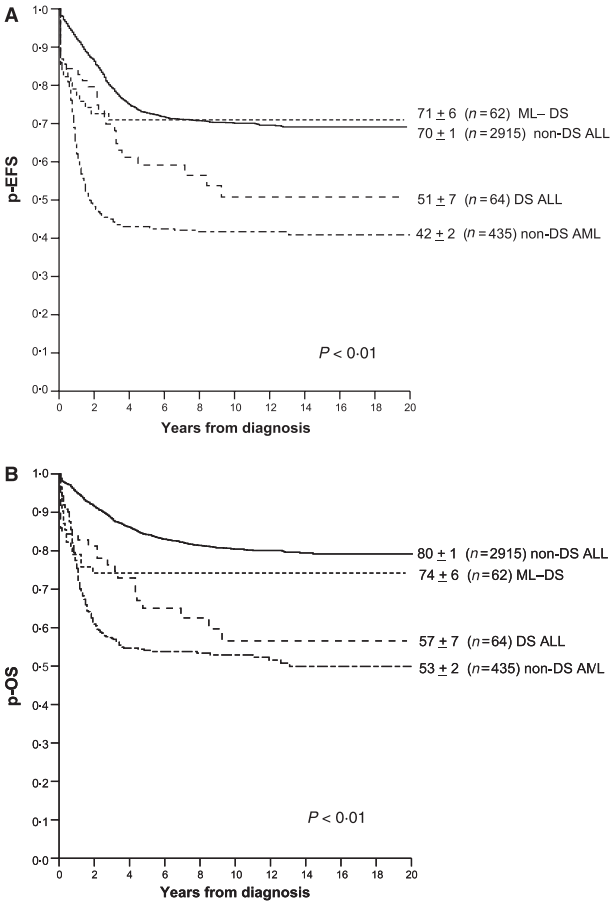

Fig 2. (A) Probability of event-free survival (at 10 years) of treated patients $n = 3476$. (B) Probability of overall survival (at 10 years) of treated patients $n = 3476$.

Cytogenetics were performed successfully in 37 of the ML-DS patients. In nine cases the karyotype was normal, while 28 patients showed clonal aberrations. The most frequent trisomies in ML-DS were gain of chromosome 8, 11 and 21. Only one patient (aged 11 years) had an aberration specific for AML: t(8;21)(q22;q22). None of the other known AML-typical aberrations was detected by G-banding analysis.

Treatment results (Table II; Fig 2A, B): DS patients carried a far better prognosis than the non-DS children [p-EFS (10 years) 71 ± 6 vs. 42 ± 2, $P < 0·01$]. The main reason was the significantly lower frequency of relapse (11·3% vs. 40·7%). The EFS for the ML-DS patients was significantly better in the second treatment period, from 1993 to 2001 (p-EFS 83 ± 6 vs. 54 ± 10, $P < 0·01$).

The p-OS results showed 5–10% higher values compared with corresponding p-EFS values. The differences were more pronounced in non-DS patients compared with DS patients mainly explained by a lower frequency of induction failures in non-DS patients.

Table III. AML: Non-Down syndrome (NDS) *versus* Down syndrome (DS).

	Non-DS	DS
Total	443	72
No therapy	8	10
Gender		
Female	228 (51·5)	50 (69·4)**
Male	215 (48·5)	22 (30·6)
Age (years)		
<1	64 (14·4)	3 (4·2)
1–<5	147 (33·2)	68 (94·4)***
5–<10	113 25·5)	0 (0)
≥10	119 (26·9)	1 (1·4)
Median (years)	5	1
WBC count ($\times 10^9$/l)		
<10	181 (40·9)	38 (52·8)*
10–<50	136 (30·7)	29 (40·3)
50–<100	58 (13·1)	3 (4·2)
≥100	65 (14·7)	0 (0)***
Missing	3 (0·7)	2 (2·8)
Median WBC	15·1	8·6
Maximum WBC	850	94
Platelet count ($\times 10^9$/l)		
<50	209 (47·2)	54 (75·0)***
≥50	220 (49·7)	14 (19·4)
Missing	14 (3·1)	4 (5·6)
Median	53	26***
Hb g/dl		
<10	353 (79·7)	53 (73·6)
≥10	82 (18·5)	16 (23·2)
Missing	8 (1·8)	3 (4·2)
Median	82	84
CNS leukaemia present	24 (5·4)	1 (1·4)
FAB type (1993–2001)		
M0	15 (6·4)	0 (0)
M1/M2	77 (33·0)	7 (18·4)
M3	12 (5·2)	1 (2·6)
M4	48 (20·6)	1 (2·6)**
M5	45 (19·3)	0 (0)**
M6	5 (2·1)	1 (2·6)
M7	15 (6·4)	25 (65·8)***
Missing/others	16 (6·9)	3 (7·9)
Cytogenetics		
Result obtained	132	37
Normal karyotype	38 (28·8)	9 (24·3)
Clonal aberrations	94 (71·2)	28 (75·7)

Results are in number (%).
Significant with *$P < 0·05$; **$P < 0·01$; ***$P < 0·001$ (chi-square test).

Discussion

This population-based study has shown high proportions of DS children in acute leukaemia, especially in AML. We have confirmed that acute leukaemia in DS children differs from the disease in non-DS individuals. In ALL, significant differences were confined to immunophenotype (absence of T cell leukaemia), cytogenetics (absence of the prognostic unfavourable translocations) and treatment results. In AML, we found a significant female predominance, and confirmed features such as the special age distribution, the predominance of FAB type M7, significantly lower platelet count and WBC at presentation and far better outcome than in non-DS patients.

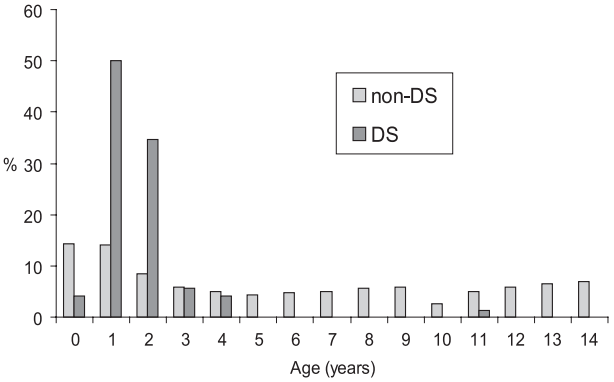

Fig 3. Age distribution (as a percentage) in 515 patients with AML without Down syndrome ($n = 443$) and with Down syndrome ($n = 72$).

In the population-based Nordic registry all patients with leukaemia, including untreated patients, are registered. Early international surveys on leukaemia in DS children were based on institutional studies, and not all of the DS patients were included. More recent studies have shown that DS children are increasingly enrolled (Lange *et al*, 1998; Chessells *et al*, 2001). In our study, the overall proportion of DS in acute leukaemia was 3·9%, compared with 2·0% and 2·1% in the two previous studies including both ALL and AML (Robison *et al*, 1984; Levitt *et al*, 1990). In ALL, we found a proportion of 2·1% of DS patients. Previous studies have reported 1·5–2·1% (Robison *et al*, 1984; Ragab *et al*, 1991; Pui *et al*, 1993; Dördelmann *et al*, 1998; Heerema *et al*, 1999; Chessells *et al*, 2001). In AML the proportion of DS was 14·0%, compared with 7–10% in other recent studies (Creutzig *et al*, 1996; Lange *et al*, 1998; Zubizarreta *et al*, 1998). A possible explanation for the high proportion of DS children in the Nordic AML studies is that these patients have been consistently included from the beginning of the study period. Even in the first trial, AML-84, DS children accounted for 17% of all patients (Lie *et al*, 1990). Differences in the prevalence of DS may play a role as well. Countries that practice the screening of all pregnancies by means of serological methods and ultrasound have documented decreasing DS live birth rates (Khoshnood *et al*, 2004). In the Nordic countries, prenatal diagnosis is only offered to mothers >35 years of age. We know that the prevalence of DS is stable in Norway and is increasing in Denmark. Higher maternal age is an important contributing factor to higher prevalence rates (Binkert *et al*, 2002; Larsen *et al*, 2002). However, it seems less likely that differences in DS prevalence rates alone can explain the observed higher DS proportion in our study.

ALL

In accordance with other reports (Robison *et al*, 1984; Levitt *et al*, 1990), the age distribution in our study was similar for non-DS and DS patients. However, we found a tendency towards a distinct age peak for the DS patients at 2 years. Due to the small numbers in the DS group this difference did not reach significance.

Down syndrome patients lacked some of the known risk factors in childhood ALL: we found no infants and no patient with T cell leukaemia (vs. 9·1% in non-DS patients). This is in accordance with previous studies (Robison *et al*, 1984; Levitt *et al*, 1990; Ragab *et al*, 1991; Pui *et al*, 1993; Dördelmann *et al*, 1998; Chessells *et al*, 2001).

Our cytogenetic findings in DS ALL patients (significantly lower frequency of hyperdiploidy, gain of chromosome X as the most common change in the modal number, none of the ALL specific chromosomal aberrations) are consistent with previous reports (Pui *et al*, 1993; Dördelmann *et al*, 1998; Chessells *et al*, 2001). Two patients had a t(8;14)(q11;q32), which has been reported to be a DS-related aberration (Forestier *et al*, 2000; Mitelman *et al*, 2004).

Treatment results for DS ALL patients have been reported to be inferior to those of the non-DS population (Dördelmann *et al*, 1998; Chessells *et al*, 2001). DS ALL patients have a higher risk of therapy-related death both during induction and in first remission (Hargrave *et al*, 2001), and it has been demonstrated that lymphoblasts from DS ALL children are significantly less sensitive to dexamethasone and asparaginase, with a similar trend for vincristine, doxorubicin and cytarabine (Frost *et al*, 2000). The greater toxicity of the treatment regimens in DS ALL patients seems to outweigh the fact that they have less adverse prognostic factors (Pui *et al*, 1993).

Our treatment results for ALL in the non-DS cohort are comparable with other international therapy studies (Gustafsson *et al*, 2000), but show a poorer outcome for the DS group (10-year p-EFS 51 ± 7 vs. 70 ± 1 in the non-DS group). This is mainly explained by a higher percentage of induction failures in DS ALL patients.

Comparing the two consecutive time periods before 1993 and 1993–2001, we found a non-significant trend towards inferior outcome for the DS patients in the second time period. In contrast, results for the non-DS children improved significantly during the same period. No general recommendations for dose reduction in DS patients were given in the protocols. Regarding the increasing induction failure rate in DS patients in the second treatment period, it can be speculated that the unsatisfying results might be because of the increased toxicity of our most recent protocol. However, results from other groups do not support a relation between modern, more intensified protocols and inferior outcome for DS patients. The UKALL studies have reported improved treatment results even for the DS group in spite of intensified therapy, with a 5-year survival rate of 78% for the latest treatment period (Stiller & Eatock, 1999). Improving the outcome of DS patients will be one of the challenges for the coming years in our ongoing new ALL study (NOPHO-ALL 2000).

AML

The age distribution of DS patients in our study confirmed that ML-DS is a disease of very young children (Creutzig *et al*, 1996; Lange *et al*, 1998; Hasle *et al*, 2000; Lange, 2000). All but one of the patients was <5 years of age. This 11-year-old girl was the only DS patient with a cytogenetic aberration specific for AML: t(8;21)(q22;q22). Her disease might be classified as a genuine 'non-DS' AML.

We found a significantly higher percentage of females in the DS group (69·4% vs. 51·5% in non-DS patients), because of a three-fold higher proportion of girls at the age of 2 years. This is in contrast to previous reports: early publications found a male predominance (Robison *et al*, 1984; Levitt *et al*, 1990; Zipursky *et al*, 1994), whereas more recent studies showed an equal sex distribution (Creutzig *et al*, 1996; Zubizarreta *et al*, 1998; Reinhardt *et al*, 2004) or a slight female predominance (Lange *et al*, 1998). Whether the considerable female predominance in our study represents a real epidemiological difference remains an open question.

Other characteristics of ML-DS, such as lower WBC and platelet counts at diagnosis and high proportion of FAB type M7 (Zipursky *et al*, 1994; Creutzig *et al*, 1996; Lange *et al*, 1998; Gamis *et al*, 2003), were confirmed in our study. Results of the cytogenetic investigation of the AML cohort have been published previously (Forestier *et al*, 2003). Our findings, of no AML-typical aberrations in DS patients aged below 5 years and gain of chromosome 8 and 21 as the most frequent numeral aberrations, are in accordance with other reports (Litz *et al*, 1995; Lange *et al*, 1998; Craze *et al*, 1999).

Several reports have described the superior treatment results in ML-DS (Ravindranath *et al*, 1992; Creutzig *et al*, 1996; Lie *et al*, 1996; Lange *et al*, 1998; Craze *et al*, 1999; Kojima *et al*, 2000). One of the possible explanations is increased sensitivity to various cytotoxic drugs (Taub *et al*, 1996; Frost *et al*, 2000; Zwaan *et al*, 2002). The present study confirms the good prognosis of DS patients. p-EFS in ML-DS was far better than that of non-DS AML (71 ± 6% vs. 42 ± 2%; $P < 0{\cdot}01$). Treatment results for both DS and non-DS patients have improved in the second time period, and the outcome in ML-DS (10-year p-EFS of 83 ± 6%) is now comparable with the best results of other published studies (Kojima *et al*, 2000; Athale *et al*, 2001; Gamis *et al*, 2003; Reinhardt *et al*, 2004).

No generally accepted recommendations for therapy modification in DS patients exist in the literature. Some have recommended confining the cumulative anthracycline dose to 240–250 mg/m^2 (Creutzig *et al*, 1996; Kojima *et al*, 2000), while others have pointed out the importance of reduced dose-intensity instead of absolute dose reduction (Gamis *et al*, 2003). The NOPHO AML treatment protocols contained no particular recommendations for DS patients. Treatment

modifications were made in many patients according to the judgement by the local oncologist. Reduced drug doses were used in 48% of the DS children. In patients receiving decreased doses the mean cumulative dose of anthracyclines and cytarabine was 75% and 67% of the protocol dose respectively (L. Abildgaard, personal communication, 2004). None of the DS patients received a bone marrow transplant. In our current protocol, we recommend reduction of the anthracycline doses to 75% and full recovery of bone marrow and general condition before starting a new course of therapy in DS patients.

The challenge for the future will be to improve the treatment outcome for DS children with ALL and reduce the treatment intensity of ML-DS to reduce the burden of toxicity without jeopardizing the favourable outcome.

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