Acute leukemia in children with Down's syndrome: the importance of population based study

The association between Down's syndrome (DS) and acute leukemia is well documented.[1-3] However, most information derives from retrospectively compiled patient series or treatment trials, which may not represent the general DS population. We report cases of acute leukemia and DS collected in the UK Childhood Cancer Study (UKCCS), a national population based case-control study. Data were gathered on all children aged 0-14 years diagnosed with acute leukemia between 1991 and 1996, irrespective of trial entry. Detailed diagnostic information on all cases was obtained from multiple sources, including: the Medical Research Council; UKCCSG; the National Registry of Childhood Tumours; the individual treating consultant; and hospital records. In addition, detailed cytogenetic information on trial and non-trial cases was obtained from the Leukaemia Research Cytogenetics Group. Molecular diagnostic information on patients with acute lymphoblastic leukemia (ALL) was provided by the central reference laboratory at the Leukaemia Research Fund Centre, Institute of Cancer Research. Details of the conduct and ethical approval of the UKCCS are described in full elsewhere.[4]

In total 1,709 children with acute leukemia enrolled in the UKCCS (Table 1). Of these, 14(6%) of the 248 with AML, and 34(2%) of the 1,461 with ALL, also had DS. Trial uptake was significantly lower for children with DS: 32/48 (67%) children with DS were in trials compared with 1,468/1,709 (86%) of non-DS cases ($p<0.01$). Entry was lowest for children with DS-AML: with only 8/14 (57%) in trials.

We also report the striking finding that the increase in AML incidence in DS was confined to FAB M6 and M7 sub-types; no other FAB types were observed. Eleven (79%) of the DS-AML cases were M7 and 3 were M6. Importantly this was not apparent initially when the provisional diagnoses recorded by the treating hospital were considered. However, following panel review for the MRC AML 10 trial, 6 of the DS-AML cases initially diagnosed at the treating hospital and recorded for trial and study purposes as AML FAB M0 (4 cases), M1 (1 case) and M2 (1 case) were reclassified as AML FAB M7 (4 cases) and M6 (2 cases). The high number of reclassifications prompted review of the non-trial cases of DS-AML. These comprised 5 cases of AML FAB M7 and one case of AML FAB M6. All 6 diagnoses remained the same after review. In contrast, taken together, M6 and M7 accounted for only 18 (8%) of non-DS AML ($p<0.001$). The mean age at diagnosis of AML was significantly lower in DS children: 2.2 years (95% CI:1.5-3.0) compared with 6.7 years (95%CI:6.1-7.4; $p<0.001$). Interestingly, the average age at diagnosis of the 18 non-DS children with AML M6 or M7 was only 3.2 years (95% CI:1.1-5.4) - comparable with DS-AML. Cytogenetic profiles in these DS-AML cases were consistent with previous reports (3;5;6). Typically, the favorable translocations associated with non-DS AML, namely t(8;21), t(15;17), inv(16), and t(1;22) typically associated with AML FAB M7, were absent. Instead, a variety of unbalanced translocations were seen: +8 in 5/14(36%) DS-AML; del(6q) in 2/14(14%); +11 in 1/14(7%) and +21 in 1/14(7%) DS-AML cases. Interestingly, both cases of del(6q) occurred in non-trial patients, emphasizing the importance of population based analysis.

We confirm that B-cell precursor ALL (BCP-ALL) is the predominant form of leukemia observed in DS,[3,7] occurring in 27/34 (79%) cases of DS-ALL compared with 1,067/1,427 (74%) cases of non-DS ALL. T-cell ALL, although reported, is extremely rare. There were no cases of proB or T-cell DS-ALL in our study. Age at diagnosis for DS- ALL and non-DS ALL were similar and the difference was not statistically significant. Whilst ML-DS is a specific entity, ALL in DS appears to be as heterogeneous as ALL in non-DS children. High hyperdiploidy (>50 chromosomes), a good-risk prognostic feature, appears underrepresented occurring in 1/27 (4%) cases. Testing for the most frequent chromosomal abnormality in childhood ALL, the *ETV6-RUNX1* fusion resulting from t(12;21), was not standard in the study period. Specific chromosomal translocations associated with adverse outcomes in childhood ALL: 11q23/MLL translocations; t(9;22); and t(1;19) were absent in DS cases. However, the numbers are small. The finding of 5/27 (19%) cases with loss of 9p is interesting; it has been suggested elsewhere that it might play a significant role in the pathogenesis of DS-ALL.[8] Two of these were in non-trial cases.

Table 1. Characteristics of children with acute leukemia with and without a diagnosis of Down's syndrome.

	Acute myeloid leukemia (AML)			*Acute lymphoblastic leukemia (ALL)*			
	Total	*Non-DS FAB M6+7*	*DS*[1]	*Total*	*Non-DS Precursor B-cell*	*Total*	*DS Precursor B-cell*
Total	234	18	14	1427	1067	34	27
Trial entry (%)	180(76.9)	14(77.8)	8(57.1)	1288(90.3)	1009(94.6)	24(70.6)	22(81.5)
Child's age at diagnosis (yrs) Mean (95% CI)	6.7 (6.1-7.4)	3.2(1.1-5.4)	2.2(1.5-3.0)	5.5(5.4-5.7)	5.3(5.1-5.5)	4.8(3.7-5.9)	4.4(3.4-5.4)
Mother's age at birth (yrs)[2] Mean (95% CI)	27.1(26.4-27.8)	27.9(25.2-30.6)	34.4(31.2-37.6)	27.5(27.2-27.8)	27.5(27.2-27.8)	31.6(29.3-33.9)	31.1(28.3-33.8)
Father's age at birth (yrs)[3] Mean (95% CI)	30.6(29.7-31.6)	31.2(28.2-34.1)	37.6(33.4-41.9)	30.6(30.3-30.9)	30.7(30.3-31.0)	33.0(30.5-35.6)	32.6(29.5-35.6)

Non-DS: non-Down's syndrome; DS: Down's syndrome. [1]All myeloid leukemia in children with Down's Syndrome were FAB M6 (n=3) or M7 (n=11). [2]12 mothers had missing ages because of the child's adoption. [3]103 fathers had missing ages.

An excess of AML FAB M7 is well documented in DS: it is a unique disease associated with a pathognomonic mutation of GATA1.[9] This report supports the separate pediatric WHO classification of myeloid leukemia of DS (ML-DS).[10] It is notable that subtypes were reclassified in 6/14(43%) cases of DS-AML. Unfortunately, this does not appear to be reflected in an earlier report of DS cases in the MRC AML 10 and 12 trials,[11] which appears to rely on the initial classifications, highlighting the importance of ensuring data is as comprehensive and up to date as possible. Here, the final AML subtypes were exclusively FAB M6 and M7. Although an apparent excess of AML M6 has also been reported, the association is not so clearly described.

A report considering trial cases alone for this period would have missed a third of all cases of acute leukemia in DS, and almost half of all cases of AML in DS. The relatively low entry of children with DS into trials limits the utility of reports solely derived from trials, emphasizing the need for a population based approach until trial entry rates have improved. Reports suggest that these are increasing, reflecting a growing recognition that children with DS may be successfully treated with intensive chemotherapy and in the context of a trial. There is a pressing need for a collaborative effort to gather data prospectively on all children with DS. The Children with Down's Syndrome Study (*www.cdss.org.uk*) is an observational cohort study set up specifically to address this need and will enable determination of the baseline characteristics of all children with DS. Furthermore, until trial entry improves, a population based approach is also imperative for the study of children with both DS and leukemia.

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Key words: acute leukemia, acute myeloid leukemia, myelodysplasia, myeloproliferative disorders, Down's syndrome.

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Kinetics of bone marrow blasts during induction and achievement of complete remission in acute myeloid leukemia

In acute myeloid leukemia (AML), bone marrow is typically examined 14 days after beginning initial induction therapy. If significant residual blasts remain, the National Comprehensive Cancer Network (NCCN) Guidelines for AML recommend re-treatment.[1] Here we examine whether bone marrow findings on day 21 might modulate the day 14 findings and thus influence the decision to begin a second course.

Our database comprised those 586 adults who had both day 14 and day 21 bone marrows (±2 days) after receiving, from 1995 to 2004, cytarabine (≥1g/m^2 per day) -con-