



Blood disorders in children with Down's syndrome: overview and update

Summary of a presentation by Professor Judith Chessells
 Leukaemia Research Fund Professor of Haematology and Oncology, Institute of Child Health
 and Honorary Consultant, Hospital for Sick Children, Great Ormond Street, London

Blood disorders are more common in children with Down's syndrome than in other children. Not only are there differences in the blood count, but leukaemia and leukaemia-like disorders also occur in excess.

The overall risk of developing leukaemia is about 18 times greater for children with Down's syndrome than for other children. It has become apparent in recent years that children with Down's syndrome respond well to the intensive treatments used for other children. It is important therefore to ensure that children with Down's syndrome and leukaemia are entered into national leukaemia trials and are managed according to full treatment protocols.

Blood count abnormalities

There are differences in blood counts between children with Down's syndrome and others particularly in the first year of life. It is important to take this into consideration when interpreting the results of laboratory investigation (Panel 1).

When investigating iron deficiency anaemia, it should be noted that the baseline mean corpuscular

Panel 1: Blood count abnormalities in children with Down's syndrome

- 64% are polycythemic for up to 2 months
- No difference between babies with and without heart disease
- Haemoglobin levels sometimes raised
- Levels of haematinics (e.g. iron, folate) normal at all ages
- Age 9–12 months MCV and MCH elevated – normal erythropoietin levels
- WBC and neutrophil counts in the low normal range
- Platelet counts raised from age 6 weeks

Leukaemia and leukaemia-like disorders in children with Down's syndrome

- Transient abnormal myelopoiesis (TAM)
 - affects 10% of newborns
 - morphologically indistinguishable from megakaryoblastic leukaemia
 - asymptomatic and usually resolves spontaneously without treatment
 - 25% develop AML later in childhood.
- Overall childhood leukaemia risk (AML and ALL)
 - increased risk maximal in the first 4 years
 - overall risk approximately 1/100 (18 times greater than in the general population).
- Acute myeloid leukaemia (AML)
 - very rare in other children (~60–70 new cases annually in children aged 0–15 years in the UK)
 - the most common leukaemia seen in children with Down's syndrome aged 1–4 years
 - usually the megakaryoblastic variant of AML
 - 150 times greater risk than in the general population.
- Acute lymphoblastic leukaemia (ALL)
 - the most common childhood leukaemia (300–400 new cases annually overall in children aged 0–15 years in the UK)
 - occurs in excess in those with Down's syndrome; highest risk aged 1–4 years.

volume (MCV) may differ from the general population. Baseline platelet count is increased, for no known reason. This is interesting as acute myeloid leukaemia (AML) in Down's syndrome often appears to be a leukaemia of platelet precursors (megakaryoblastic).



Transient abnormal myelopoiesis (TAM)

- TAM is almost unique to Down's syndrome, and probably occurs in about 10% of newborn infants. This condition, where blast cells are found in the blood and bone marrow, is morphologically indistinguishable from megakaryoblastic leukaemia. TAM is usually asymptomatic and often resolves spontaneously without treatment but may occasionally persist for several months. On rare occasions, low doses of cytotoxic drugs may be required to reduce the blood count (Panel 2).
- Most neonates with TAM recover and remain well, however, about 20–25% subsequently develop AML. A very small proportion of children with TAM may die *in utero* from hydrops or perinatally due to liver fibrosis. The reasons for this are still not understood.
- Following diagnosis, the blood count is usually checked monthly for 2–3 months – if normal, no further action is needed. If AML develops subsequently, it will declare clinically in the usual manner.
- All information must be shared with parents. The unpredictability is hard for them to cope with. They can be told that 75% of children do not develop AML. If it does develop, it will be within the first two years. It is very chemosensitive and treatment is more successful than for other children (see later).
- Recent research suggests that leukaemias are associated not only with genetic changes, but also with cytogenetic changes. Clonal cytogenetic abnormalities can occur in children with Down's syndrome and TAM just as they

Panel 2: TAM case studies

The most common TAM scenario involves a baby with Down's syndrome who has had a blood count for some other reason. Although the actual blood count values are normal, numerous odd blast cells are seen on the film. The baby is completely well. No intervention is needed. The blood count returns to normal within a few months.

A more unusual scenario is illustrated by an infant who was born at 37 weeks gestation with Down's syndrome and perimembranous VSD. The leukocyte count was found to be very high ($471 \times 10^9/l$), and 90% of the count were blast cells indistinguishable from AML blast cells. The baby was unstable and there were problems with hydration and ventilation. In order to avoid thrombotic problems, cytotoxic treatment with a very small dose of cytarabine was given, and the count slowly improved. The cardiac defect was repaired and the infant has been well ever since with no sign of acute leukaemia.

occur in any type of leukaemia – and yet they get better without any treatment. The reason for this is unknown.

Childhood leukaemias

The issue of leukaemia in children with Down's syndrome is interesting not least because it illustrates the dramatic change over the past 20 years or so in the perception of families and paediatricians as to what is appropriate and what standard of treatment is required. Contemporary UK practice is not only that these children should be treated, but that they should be intensively treated and also entered into all national trials.

The overall risk of childhood leukaemia (AML and ALL) is around 1/100, which is 18 times higher than in other children. It is greatest in children aged 0–5 years, with no cases over 29 years. There is a very specific risk of myeloid leukaemia which for under fives is 150 times that in other children. The response to treatment of both AML and ALL is good.

Increased susceptibility to infection leads to increased morbidity and mortality during treatment for leukaemia. The infection risk may be linked to underlying immunological deficits.

All children in the UK who acquire any type of cancer have their health records flagged and the data entered on the register at the Childhood Cancer Research Group in Oxford. The UK Children's Cancer Study Group (UKCCSG) can then link data from the register with records held by specialist paediatric oncology centres. Hence, levels of referral can be determined.

When children with Down's syndrome who had leukaemia were investigated in this way, it was revealed that many fewer than expected were being referred to specialist services. Therefore information as to how they were faring was sought from the MRC National AML trials (AML 10, 1987–95 and AML 12) which were examining the role of short term very intensive cytotoxic chemotherapy and from the MRCALL trials (UKALL X, 1985–90, and UKALL XI, 1990–97).

Acute myeloid leukaemia (AML)

AML is the most common leukaemia seen in children with Down's syndrome. Panel 3 summarises findings from the UK trials AML 10 and 12.

The risk of increased deaths from infection during induction and remission means that there has to be very good supportive and nursing care. There must also be extreme vigilance as these children are vulnerable to life-threatening infections during their treatment although they do have a very good chance of cure and a very low risk of relapse.

AML in children with Down's syndrome is quite an indolent disease. Clinical problems may be slow to

Panel 3: Review of findings from AML 10 and 12

- Fewer children with Down's syndrome entered than expected, suggesting continued reluctance to enter children with Down's syndrome into national trials.
- Initial remission rate following induction slightly poorer (not significant) in children with Down's syndrome compared to others (83% vs 92%).
- Deaths during induction significantly increased (17% vs 4%).
- Overall 5-year survival the same for children with and without Down's syndrome (59% vs 60%).
- Relapse risk significantly less than for children without Down's syndrome (8% vs 39%).
- Risk of death in remission significantly greater than for children without Down's syndrome (21% vs 8%) because of increased vulnerability to infection during intensive chemotherapy.
- Different morphological type (megakaryoblastic) in Down's syndrome than in other children (usually monoblastic or myeloid).
- Chromosome 15;17 and 8;21 translocations in leukaemic cells, which are known to have good prognoses, do not occur in children with Down's syndrome. Despite this patients tend to do well.

Panel 4: AML case study

Alex was living with his family overseas when, at age 10 months, he was found to have blast cells in his blood. His family did not return to the UK until 4 months later by which time he was starting to get anaemic and had some bruising, hence intervention was necessary. He was treated according to the standard full protocol and has done very well since.

develop. There is plenty of time to investigate and discuss treatment options. Intervention is not necessary until either symptoms become apparent or blood products are needed (Panel 4). Eventually however, the disease will progress and without treatment death will ensue.

Children with Down's syndrome and AML respond unusually well to intensive treatment. The need for aggressive cytotoxic chemotherapy has been questioned and debated worldwide. Some do well on less intensive regimens but some die. An international trial would be necessary to establish whether it is indeed safe to use less intensive protocols.

In the early days of the AML trials, four children with Down's syndrome had bone marrow transplants (BMT). However the excellent response to intensive cytotoxic therapy which is now reported suggests that

BMT should no longer be necessary for any child with Down's syndrome.

In summary, children with Down's syndrome get a unique form of myeloid leukaemia – megakaryoblastic leukaemia – which is extremely rare in other children. It is very sensitive to aggressive chemotherapy, which gives a high chance of cure. BMT is not needed as these children do very well on chemotherapy.

Acute lymphoblastic leukaemia (ALL)

Modern treatment for ALL extends for much longer than for AML. It comprises:

- Induction and intensification therapy to achieve stable remission
- Intrathecal methotrexate to prevent leukaemic relapse in the spinal fluid
- Then at least two years of outpatient immunosuppressive treatment with oral mercaptopurine and methotrexate.

A review of the findings from two recent national MRC trials, UKALL X (1985–90) and UKALL XI (1990–97) is shown in Panel 5.

Although the relapse risk in most reports is similar, the overall survival for children with Down's syndrome

Panel 5: Review of findings from UKALL X and UKALL XI

- More children with Down's syndrome were entered in the UKALL XI trial but it is probably the case that not all were entered or adequately treated.
- Significantly more children with Down's syndrome and ALL were aged between 2–9 years compared with other children i.e. fewer infants and teenagers.
- All children with Down's syndrome who developed leukaemia had early B cell leukaemia – common lymphoblastic leukaemia. As shown in previous studies, there were no cases of T cell leukaemia.
- Cytogenetics were unremarkable with absence of both good (e.g. high-hyperdiploid ALL) and adverse (e.g. 9/22 translocation) prognostic factors.
- The response to treatment showed a steady improvement in the children with Down's syndrome. The risk of death in the first remission during treatment fell from 21% to 8% from UKALL X to UKALL XI. For children without Down's syndrome, the risk fell from 4% to 2%.
- The overall 5-year survival for children with Down's syndrome was good (73%) but significantly worse than for children without Down's syndrome (82%). UKALL XI figures are better than UKALL X (Figure 1).

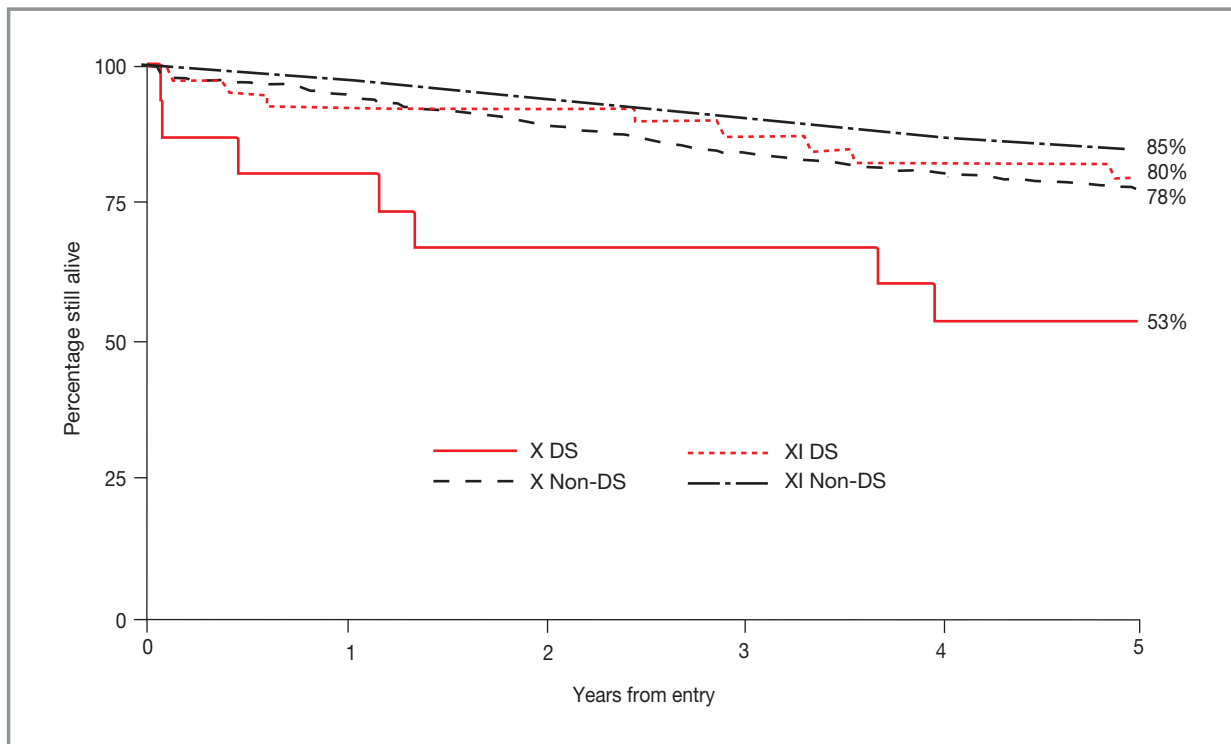


Figure 1: Overall survival for children with Down's syndrome in UKALL X (DS vs non DS $p < 0.001$) and XI (DS vs non DS $p = 0.1$).

compared with children without Down's syndrome was not quite as good as in some reports. Treatment-related deaths tended to follow long periods of neutropaenia when children had been on long-term antibiotics. They tended to be fungal infections, which raises the question as to whether aggressive antifungal therapy with amphotericin should have been administered earlier.

During oral continuation therapy, patients are at risk of ordinary childhood illnesses such as chicken pox. As with AML, it is important to deliver chemotherapy as intensively as possible and also to provide very good supportive care to reduce the risk of treatment-related deaths.

Other cancers

In contrast to the leukaemias, in Down's syndrome there is a significantly decreased risk of solid tumours in all age groups with the possible exception of testicular and ovarian cancers.

Summary

- Children with Down's syndrome have macrocytosis and thrombocytosis, which is apparently unrelated to congenital heart disease.
- They have a variable degree of immune deficiency.
- There is an almost unique risk of transient neonatal abnormal myelopoiesis (TAM) which usually follows a benign course.
- Acute lymphoblastic and myeloblastic leukaemias are more common in children with Down's syndrome

than in other children. Both respond remarkably well to intensive cytotoxic chemotherapy.

- Entry into national UK trials should be improved and national treatment protocols followed.
- There is a need for maximal supportive care during induction and remission because of the increased risk of infection.

Further reading

- Chessells JM, Harrison G, Richards SM et al. Down's syndrome and acute lymphoblastic leukaemia: clinical features and response to treatment. *Arch Dis Child* 2001;**85**:321-5
- Craze JL, Harrison G, Wheatley K, Hann IM, Chessells JM. Improved outcome of acute myeloid leukaemia in Down's syndrome. *Arch Dis Child* 1999;**81**:32-7
- Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. *Lancet* 2000;**355**:165-9
- Levitt GA, Stiller CA, Chessells JM. Prognosis of Down's syndrome with acute leukaemia. *Arch Dis Child* 1990;**65**:212-6
- Robison LL, Nesbit ME, Sather HN et al. Down's syndrome and acute leukemia in children: a 10-year retrospective survey from Children's Cancer Study Group. *J Paediatr* 1984;**105**:235-42

A complete transcript of this presentation, together with references, is available at www.dsmig.org.uk.