Childhood Leukaemia – Other Factors

All the references (Author year) in this article are listed alphabetically by author in "Childhood Leukaemia Articles References". Where the year is in blue, and underlined, it is a hyperlink to the pubmed entry.

Other factors linked with childhood leukaemia

General

Ou (2002) found that the risk of pre-B-cell ALL increased with advanced paternal age, younger and advanced maternal age and high birth order, and T-cell ALL was associated with high birth weight and a history of induced abortion. The author concluded that *"the association of ALL with birth characteristics and maternal reproductive factors varies with the immunophenotype of the ALL."*

However, most studies have not looked at specific phenotypes, not always differentiating between ALL and AML (often because of the small numbers of children involved), and so it is difficult to gain a clear idea of what other factors may be important in the development of specific leukaemia subtypes.

Parental

Parental age

Most studies have observed an increased risk for childhood leukaemia with advanced maternal age (Schüz 1999, Reynolds 2002, Johnson 2009), advanced paternal age (Ou 2002), or advanced parental age for leukaemia (Dockerty 2001), especially under the age of 5 (Yip 2006), although Ou (2002) reported a risk association in ALL with young maternal age. Ross (1997) found that infant AML was associated with increased maternal age.

Maternal

Reproductive history

A maternal history of previous miscarriages is a frequently reported risk factor for development of ALL – and in some cases AML – in a subsequent child (Kaatsch 1996, Perrillat 2002, Hernández-Morales 2009). Yeazel (1995) found that a previous history of foetal loss was associated with leukaemia diagnosed before the age of 4 and especially before the age of 2. One previous foetal loss increased the risk for ALL and AML by 5 times and 2 or more losses increased the risk for ALL by 25 times and AML by 12 times. The authors concluded *"Childhood acute leukemia occurring at younger ages may be associated with an underlying genetic abnormality or chronic environmental exposure, which can be either lethal to the developing fetus or mutagenic and result in the development of acute leukemia."* Ma (2005) found a link between multiple miscarriages and an increased rate of infant leukaemia. Ou (2002) found that an induced abortion prior to the index pregnancy increased the risk of a leukaemia diagnosis for children under 2.

Molar pregnancy has been associated with ALL, in the large UKCCS study though the numbers were small (Roman 2006).

There was an increased risk of AML in children with Down syndrome for parents who had tried for a year or more to become pregnant (Puumala 2007). Hormone treatment for infertility (Schüz

1999) or oral contraceptive use during the index pregnancy (Ou 2002) was also found to increase the risk of acute leukaemia.

Pregnancy

Ognjanovic suggested that some maternal health conditions during pregnancy may be relevant in childhood leukemogenesis, when the child also has Down syndrome. Her 2009 study reported that vaginal bleeding was associated with a reduced risk of leukaemia, whilst amniocentesis was associated with an increased risk of AML.

Antibiotic use

ALL and AML have both been associated with maternal antibiotic use (Kaatsch 2010). The authors of the study were uncertain as to whether this link may have been to the underlying infection rather than the treatment.

Diet

Increased risk of childhood leukaemia has been associated with DNA topoisomerase inhibitors. This includes some drugs used in chemotherapy, benzene metabolites (from air pollution and cigarette smoke), certain fruits, tea, coffee, wine, soy and cocoa and many other substances (Greaves 1997, Gilliland 2004). Menegaux (2005) found that maternal coffee drinking during pregnancy increased the risk of ALL, the risk increasing with increased consumption. Topoisomerase inhibitors inhibit DNA repair and are strongly associated with one of the chromosome rearrangements common in infant leukaemia (Alexander 2001, Greaves & Wiemels 2003) or AML (Ross 1996, Spector 2005). Petridou (2005) reported that ALL risk was higher for children born to mothers who ate more sugars and syrups, and meat and meat products. N-nitroso compounds (found in cured meats and hot dogs) have been linked with childhood leukaemia in at least one study (Peters 1994).

Hypertension

Hypertension has been linked with AML in one study (Cnattingius 1995).

Neonatal period

Zack (1991) found associations between various factors at birth and an increased risk of leukaemia; these included exposure to nitrous oxide anaesthesia during delivery; children with a cleft lip or palate; difficult labour but unspecified complications; uncomplicated physiological jaundice; receiving supplemental oxygen, with "*other conditions of the fetus or newborn,*" and neonatal jaundice (Hernández-Morales 2009).

Gender

That the incidence of ALL in boys and girls is different is well established, with boys being more likely to develop ALL than girls (Zahm & Devesa 1995, Pearce & Parker 2001, Johnson 2008), although the incidence of girls is often higher among young children (Gurney 1995, Ross 1997). Males tend to have a worse prognosis (Eden 2000). Adelman (2007) found that boys (but not girls) had an elevated risk of developing ALL in areas of relatively high re-location rates.

Ethnicity

Incidence of ALL is significantly lower among black children in the US (Gurney 1995, Reynolds 2002, Adelman 2007, Johnson 2008) and Africa, and mixed race children in South Africa and Chile (Greaves 1993). During the first few years of life, the incidence rate of AML among African American children is approximately ⅓ the rate of Caucasian children; however, African American children ≥ 3 years of age have higher rates than Caucasians. Hispanics had a higher incidence of ALL, particularly in childhood, in a study by Yamamoto (2008), but there were differences in incidence, depending on the subtype (Aldrich 2006).

However, for many adult cancers, ethnicity seems less important than the country you are living in and the adopted lifestyle, as the incidence levels in immigrants generally begins to resemble that of the indigenous population in the country they are living in – certainly in subsequent generations. A study by Spallek (2008) found that children born in Germany into a family of Turkish descent (as determined by name) had no increased risk of developing leukaemia than children of German descent.

Caesarian section

In one study that looked at potential links with leukaemia, Cnattingius (1995) found an association with AML.

Resuscitation

Very little mention has been made of this as a risk factor. However, Naumberg (2002) suggested that resuscitation with 100% oxygen with a facemask and bag directly postpartum was associated with increased risk of childhood lymphatic leukemia and Spector (2005) found a 3-fold increase in risk in childhood cancer if oxygen was administered for 3 minutes or more.

Head size

Though rarely assessed, children with leukaemia have been found to have a significantly smaller head circumference than control children (Méhes 1985).

Apgar score

1-minute Apgar scores of less than 7 increased risk of ALL and AML (Johnson 2008).

Birth marks

Mertens (1998) found a higher reported frequency of birthmarks in both those with ALL and those with AML, or childhood cancer in general (Johnson 2007).

Birth order

Being the first born child has been associated with increased risk of leukaemia (Kaye 1991, Kaatsch 1996, Dockerty 2001), especially between the ages of 1 and 5, although the opposite has also been reported (Ou 2002). Kaye's team had found that not just firstborns, but those with the next oldest sibling more than 5 years older had an increased risk. Jourdain-Da Silva (2004, Altieri 2006) found that having many siblings increased the risk of ALL, but Altieri found if they were older, the risk was significantly decreased. Westergaard (1997) found that the risk of ALL went

down with increasing birth order, whilst the risk for AML went up, especially for a diagnosis at 2 or 3 years of age.

Infante-Rivard (2000) found that having a school age sibling during the first year of life was significantly protective for those older than 4 years at the time of diagnosis, whereas having a school age sibling at the time of diagnosis significantly increased the risk in all children, but most markedly in those diagnosed before 4 years of age.

Birth order is used as a proxy for infection as it is assumed that children in larger families – especially those lower down the birth order – are exposed to more infections in early childhood. A number of studies have reported results but there is little consensus. Of 13 recent case-control studies, five showed an increased risk of childhood leukaemia in larger families, seven found no effect and two showed a protective effect. The different results of the studies may reflect some impact of changing social conditions in the countries studied, and over time.

Birth weight

Circulating IGF levels are highly correlated with foetal growth, and IGFs are believed to play an important role in carcinogenesis. However, the exact mechanism by which these two factors may be linked has not been clearly established (Callan 2009).

Birthweight of 3,000 grammes or more (Westergaard 1997, Ou 2002, Paltiel 2004, Podvin 2006, Johnson 2008, Spix 2009, Rangel 2010) is associated with an increased risk of ALL, and AML (McLaughlin 2006, Caughey & Michels 2009). Hjalgrim's meta-analysis of 18 studies (2003) concluded that for each 1 kg increase in birthweight, the risk of ALL increases by 14% and AML risk increases by 29%. Being heavier at birth has been associated with infant leukaemia diagnosed between 6 months and 1 year (Ross 1997), before the age of 2 (Yeazel 1997), especially for children with AML, and Robison (1987) found that weight over 3800 gms significantly increased the risk of ALL for children diagnosed before the age of 4, but not later. Schüz (1999) found an increased risk of acute leukaemia with weights above 4,000 g *and* below 2,500g.Westergaard suggested that "*a plausible explanation may be that increasing birth weight is associated with a higher rate of cell proliferation and/or a larger number of precursor cells being at risk of malignant transformation.*" Caughey & Michels (2009) found low and high birthweight was associated with AML, suggesting that the risk is elevated at both extremes, a U-shaped association.

McLaughlin (2006) found that high birth weight was associated with ALL only when the mother was not overweight, whilst heavier maternal weight was associated with ALL only when the infant was not high birth weight. Increased pregnancy-related weight gain was associated with ALL. For AML, birth weight under 3,000 grammes and higher pre-pregnancy weight were both associated with increased risk. These findings suggest that childhood leukaemia may be related to factors influencing abnormal foetal growth patterns.

L Milne reported (2008) "*Most studies of the association between birth weight and risk of childhood ALL have reported positive associations, while results have been less consistent for AML. Few studies have taken account of gestational age in the analysis of birth weight. As birth weight is a function of both intrauterine growth and length of gestation, it is not possible to differentiate between an association with high birth weight per se and an association with accelerated intrauterine growth, without accounting for gestational age.*" In a recent analysis she found that it is accelerated growth, rather than high birth weight (Milne 2007, 2009, Sprehe 2009) that is involved in the causal pathway for ALL. This did not seem to be true of AML. Foetal growth she sees as determined by a mixture of genetic, nutritional and hormonal factors, possibly with a role for insulin-like growth factor in the causal pathway.

Childhood

Diet

Hamburgers eaten once a week or more doubled the risk of ALL (Sarasua & Savitz 1994), and was greater if the child did not take vitamin supplements. The author believed *"there was a possible adverse effect of dietary nitrites and nitrosamines".*

It has been suggested (Lachenmeier 2010) that infant carrot juice contains substances that may act as precursors for benzene formation during food processing. Benzene exposure has been linked to childhood leukaemia. The authors concluded that the risk was very low, though care should be taken to reduce contaminants to as low levels as reasonably achievable.

Other

Residential status

The Petridou study (1997) found differences in spatial clustering as to urban, semi-urban or rural places where children live. Children younger than 10 years old, living in an urban environment had an increased risk of developing leukaemia, and Petridou concluded that localised environmental exposures could contribute to the aetiology of childhood leukaemia. This may have relevance to a theory of infection, and there may be other factors at work as well.

There was a statistically significant increase in the rate of leukaemia and brain / CNS tumours reported in South and North east Florida (Amin 2010). The authors concluded *"This evidence is suggestive of the presence of possible predisposing factors in these cluster regions."*

Socioeconomic status

Incidence of ALL is higher in areas of high social class (Alexander 1991, Stiller & Parkin 1996, Dockerty 1999, Borugian 2005, Draper 2005), though A. Smith (2006), analysing the large UKCCS study found no effect, and neither did Swensen (1997), and Adam (2008), in a literature study, suggests any such link is likely to be weak, possibly more significant at the birth of the child, than later. Smith suggested that previous studies varied because of the statistics used to analyse the result. This is always a problem with the small number of children concerned.

However, evidence from developing countries suggests that incidence of ALL in children aged 1-4 years is rising with improved socioeconomic conditions (Hrusák 2002).

Seasonal variation

Higgins (2001) found significant links between leukaemia and month of birth, for those born before 1960, and month of diagnosis for those diagnosed before 1962. Seasonal variations at diagnosis have also been found (Westerbeek 1998, Ross 1999, Karimi & Yarmohammadi 2003). Feltbower (2001) found variations according to birth area; and HT Sørensen (2001) found an April birth peak for leukaemia diagnosis in the under 4s. Other studies found no variation (Kajtár 2003). The variations may be proxies for infections which can have seasonal peaks of occurrence.

Environmental factors

Water

Cocco (1996) found that having a well in the backyard increased the risk of ALL. This was in one town in Sardinia, so there may have been something specific to the local water.

Geopathic stress

This is recognised in many countries as being a significant factor in the development of cancer, which is likely to include childhood leukaemia. Geopathic stress lines are not recognised by most main-stream scientists, as it has not been determined what physical attributes they have. They are usually detected by "dowsing". However, peer-reviewed papers are available that show that good dowsers are better at finding drinkable water than scientists using the latest geophysical surveying tools, although it is not known why this is. There are also papers linking geopathic stress lines with various cancers (referenced in Bachler 1976).

Possible protective factors in childhood leukaemia

Multiple births

Being one of twins may reduce the risk of leukaemia (Murphy 2008), though not necessarily so (Cnattingius 1995). The reason for any possible risk reduction is unclear.

Diet

Evidence from one study suggests that there is a strong protective effect of consumption of oranges and bananas in early life (Kwan 2004). Other studies (Jensen 2004, Petridou 2005, McNally & Parker 2006) have suggested that consumption of fresh fruit and vegetables generally have a protective effect, independent of the child's diet up to age 2 years (Kwan 2009). Petridou also found a decreased risk with maternal consumption of fish and seafood. Jensen thought that dietary carotenoids and glutathione appeared to be important.

Curcumin and turmeric have been shown to inhibit cancer (Alaikov 2007) (including childhood leukaemia) at initiation, promotion and progression stages of development (Nagabhushan & Bhide 1992, 2004) in different ways (Blasius 2007).

Supplements

Maternal use of vitamins, cod liver oil, folate and iron supplements have been associated (Shu 1988, Wen 2002, Schüz 2007) with a decreased risk of ALL, although children's vitamin intake was found to increase the risk of leukaemia (MacArthur 2008), especially AML, if multivitamins were taken during the first year of life or for an extended period of time (Blair 2008). The timing seems to be particularly critical as Ross (2005) found that vitamin use before the index pregnancy reduced risk for ALL, as did Milne (2009), but not AML, and increased the risk of both if taken during pregnancy. It is believed that inadequate folate may cause the first 'hit' in the leukaemia pathway, or prevent the child repairing the first or subsequent hits.

Folate metabolism is thought to be important in the development of leukaemia. There is some evidence to suggest that maternal folate supplementation during pregnancy may protect against childhood leukaemia (Thompson 2001), though Dockerty (2007) both in the team's own New

Zealand study, and in their meta analysis, including results from Australia and Canada did not find evidence to support Thompson's hypothesis. There are differences in the way that individuals metabolise folate and this may be important (Wiemels 2001). Koppen (2010) concluded that *"susceptibility to (childhood) ALL is partly related to constitutional differences in folate gene polymorphisms" (*supported by Lightfoot 2010) and that some polymorphisms in the MTHFR gene were associated with a decreased susceptibility to childhood ALL in non-Asian populations.

Infectious exposure

Children attending day care are less likely to develop leukaemia (Petridou 1993, Perrillat 2002, Jourdan-Da Silva 2004, Gilham 2005, Ma 2005, Kamper-Jørgensen 2007, Urayama 2010), particularly common B-cell precursor ALL (c-ALL)(Urayama 2008). It was assumed that attendance increased their exposure to infections, strengthening the immune system. In fact Gilham (2005) found that any social activity outside the family in the first year of life significantly reduced the risk of ALL, and Spix (2009) found this protective effect continued until the 5th year. Perrillat found that day-care without developing infections, did not offer a protective effect; neither did infections without the day-care, although Canfield (2004) did. However, several studies have reported no protective effect (Roman 1994, Petridou 1997, Rosenbaum 2000, Chan 2002). Older siblings (Infante-Rivard 2000, Jourdan-Da Silva 2004), or the number of infectious episodes (Neglia 2000, Perrillat 2002) had a protective effect.

The different conclusions may indicate that there are important confounders that have not been adequately considered, or we need to question whether day care attendance is a reliable proxy for infectious exposure.

Ma (2005) found that parentally reported ear infection during infancy was associated with a significantly reduced risk of ALL in non Hispanic white children. They highlight an important ethnic difference but it is not clear whether this may be due to cultural/environmental factors or biological characteristics.

If an abnormal immune response to an infection is a key step in the development of childhood leukaemia then there may be associations to be found with other abnormal immune responses, for example allergy or atopy. A history of allergies (including asthma, eczema hay fever, food or drug allergies, or hives) has been found (Nishi & Miyake 1989, Petridou 1997, Schüz 1999, 2003, Wen 2000, Jourdain-Da Silva 2004, Rosenbaum 2005, Hughes 2007) to have a protective effect against leukaemia, even amongst siblings (Wen 2000). As always, the research is not unanimous and a late history of asthma (Spector 2004) was found to increase the risk of leukaemia, or allergies in general were linked to a specific type of leukaemia (Buckley 1994). A review by Linabery (2010) of 10 case-control studies concluded that both ALL and AML were associated with atopy/allergies, and inverse associations with asthma, eczema and hay fever and ALL.

The evidence suggests that early childhood infections in general, within the first two years of life, are protective, whereas infections in later life may not be.

Prescription medication use

Some medications were found to be negatively associated with infant leukaemia (Ross 2003). These were prescribed for a variety of reasons and the mechanism of protection therefore is unclear. Actual medical records were used, so recall bias would have played no part in the findings.

Breast feeding

There is a fairly substantial body of evidence pointing towards a protective effect of even short-term breast feeding (Shu 1999a, Perrillat 2002, McNally & Parker 2006, MacArthur 2008). A meta-analysis reported a relative risk of 0.76 (Kwan 2004). Shu found that the reduction in risk was stronger with a longer duration of breast-feeding.

A study looking at the relationship of breast feeding with Hib infection (Silfverdal 1997) suggested that breast feeding acts in a manner similar to vaccination, stimulating the immune system. It could therefore provide a protective effect against childhood leukaemia. MacArthur (2008) also suggested this possibility as the use of immunosuppressant medication by children decreased leukaemia risk.

There have been concerns about various practices in the past that have largely been cleared as leukaemia risks. These include the following:-

Human Growth Hormone (GH)

After more than 20 years, leukaemia, a major safety issue initially believed associated with GH, has not been confirmed (Bell 2010).

Ultrasound scans

Concerns arose in the early 1980s about potential links between ultrasound scans in pregnancy and a potential increased risk of childhood leukaemia.

There has been little evidence that i*n utero* diagnostic ultrasound tests are linked with an increased risk of childhood leukaemia (Petridou 1997), either ALL (Cartwright 1984, Petridou 1997, Naumburg 2000, Shu XO 1994, 2002), or Acute Non-lymphocytic Leukaemia, ANLL (Van Duijn 1994), although Naumburg found a small increase in risk for ultrasound scans carried out in the second trimester of pregnancy. Dr Razum in Germany did a re-analysis of the Naumburg results and suggested that her data was consistent with the probability that a small proportion of cases of childhood leukaemia might be attributable to prenatal ultrasound exposure.

Kinnier Wilson (1984) found no evidence of an increased risk and suggested that *"the observed difference between cases and controls exposed during the earlier years of ultrasound use may be due to the selective application of this technique to abnormal pregnancies at that time".*

Ultrasound exposure, *in vitro*, has been shown to cause membrane changes (Dinno 1989), and some studies have shown an association between ultrasound exposure and left-handedness in boys (Kieler 1998, Salvesen 1999, 2002), which could show that foetal development can be affected, possibly in ways that have not been looked at.

Although the risk levels are small and contested, ultrasound scans as a form of "baby TV" should not be routine, but be used for diagnostic or therapeutic use. There is concerning evidence of links between ultrasound scans and autism. The HPA states that there have been some reports suggesting possible neurological effects on the unborn child. The concern is that with souvenir scans the beam of ultrasound stays static over the baby's head for longer in order to get a sharp mug shot.

Vitamin K injections

Since the 1960's vitamin K has been used widely in the UK, throughout Europe and the US, being given as a single injection just after birth. This is a cheap and effective way of avoiding vitamin K deficiency, a rare but serious condition, with no recorded treatment failures, even in babies with liver disease, who are at most risk.

In the 1990s 2 papers were published in the medical literature, suggested that intra-muscular vitamin K injections significantly increase children's chances of developing childhood leukaemia (Golding 1990, 1992). Research carried out by Parker (1998) found a very slight increase in risk for children developing ALL.

Follow-up international studies, reviewed by Roman (2002) found no evidence to support these findings, and a joint UK Medicines Control Agency, Committee on the Safety of Medicines and Department of Health expert group has concluded that overall, the available data do not support an increased risk of cancer, including leukaemia, caused by vitamin K.

Discussion

With the increase in knowledge about the subtypes of childhood leukaemia and the genetic changes that characterise them, it would seem that it may become easier to determine what factors will add to or decrease the risk of developing particular types of leukaemia. However, due to the fortunate rarity of the illness, the numbers of children with specific phenotypes is going to make this information difficult to obtain, without significant international co-operation, extensive funding for such studies and shared protocols, to ensure that the same things were being investigated. Even then, important factors or, indeed co-factors, could easily and accidentally be omitted from studies.

Many of the factors discussed above shed some insight, perhaps, on the sort of environmental exposures that could be avoided, in order to prevent an increased likelihood of developing leukaemia and the potential for relapse in children recovering after treatment.