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HYPOTHESIS

Big babies and infant leukemia: a role for insulin-like growth factor-1?

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Several epidemiologic studies have demonstrated that high birthweight is associated with an increased risk of infant leukemia; however, the reason for this relationship is unclear. Biologic data demonstrate that birthweight is correlated positively with circulating levels of insulin-like growth factor-1 (IGF-1). IGF-1 is important in blood formation and regulation and has been shown to stimulate the growth of both myeloid and lymphoid cells in culture. Since infants who develop leukemia are likely to have had at least one transforming event occur *in utero*, we hypothesize that high levels of IGF-1 may both produce a larger baby and contribute to leukemogenesis. *Cancer Causes and Control,* 1996, 7, 553-559

Key words: Birthweight, childhood, IGF-1, infant, leukemia.

Introduction

The majority of epidemiologic studies of childhood leukemia have shown that there is an increased risk of leukemia (approximately twofold) in high birthweight babies, or a deficit of low birthweights among leukemia cases (Table 1).[1-7,10-11,13,15-16] Moreover, many of the statistically significant associations have been confined to younger children, particularly those diagnosed at less than two years of age.[6-7,15-16] In earlier studies, some of the positive associations have been found only in males[5] or have reached statistical significance only in females.[3,4,7] However, it is difficult to evaluate these gender associations since it is unclear how many cases were infants. In particular, it is important to note that infant leukemia is more common in females, whereas childhood leukemia overall is more common in males.[17] A minority of studies[8,9,12,14] have failed to demonstrate an association between high birthweight and risk of leukemia. Some earlier studies ascertained cases through death certificates.[1-4,9] Since it is unknown whether children with higher birthweights experience a better prognosis, this method of case ascertainment could bias the odds ratio toward the null. Overall, we suggest that there is compelling evidence to indicate that high birthweight is a risk factor for infant leukemia.

Increased birthweight also has been associated with other childhood malignancies including Wilms' tumor, neuroblastoma, and astrocytomas.[18] In a recent analysis of over 1,800 children in the National Wilms' Tumor Study, investigators reported that children with Wilms' tumor weighed significantly more at birth than did newborns in the general population.[19] Babies with Beckwith-Wiedemann syndrome (BWS) have generalized macrosomia and associated high birthweight, and have a greatly increased risk of Wilms' tumor over the general population. Patients with BWS recently have been shown to have biallelic (as opposed to the normal monoallelic) expression of insulin-like growth factor II (IGF-2).[20] Biallelic expression of IGF-2 also has been demonstrated

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Table 1. Epidemiologic studies examining birthweight and childhood leukemia

Author (year)	Study type (n = leukemia cases)	Definition of high birthweight	Birthweight findings with leukemia (comments)
MacMahon (1962)[1]	Birth and death certificates: childhood cancer overall and by leukemia (n = 1,323)	Not applicable[a]	Positive association; no age stratification provided
Iversen (1966)[2]	Birth and death certificates: leukemia only (n = 258)	Not applicable[a]	Deficit of low birthweights in children with leukemia
Jackson (1968)[3]	Twins: leukemia only (n = 50)	Not available	Nearly 70 percent of the leukemic twins were heavier than the non-leukemic co-twin[b,c]
Fasal (1971)[4]	Case-control: leukemia only (n = 802)	Males (> 9 lb); Females (> 8.5 lb)	Overall odds ratio (OR) = 1.40; males 1.10, females 2.07[d]
Wertelecki (1973)[5]	Sibships: leukemia only (n = 72)[e]	Not applicable[a]	Higher birthweight ranks for cases within sibships[f]
Hirayama (1980)[6]	Tumor registry: childhood cancer overall and by leukemia (n = 4,421)	> 4000 g	For cases < 2 years of age at diagnosis, statistically significant higher risk (69%) compared with cases who weighed ≤ 3400 g
Daling (1984)[7]	Birth certificates and cancer registry: childhood cancer overall and by leukemia (n = 681)	> 4000 g	For cases < 2 years of age, positive association[b,d]
Shaw (1984)[8]	Case-control: leukemia only (n = 255)	Not applicable[a]	No association; no age stratification provided
Eisenberg (1987)[9]	Birth certificates and death certificates: childhood cancer overall and by leukemia (n = 1,304)[e]	Not applicable	No association when examining trends for younger age leukemias (including infant deaths, or 1-10 years of age at death)
Shu (1988)[10]	Case-control: ALL and AML[g] (n = 309)	> 3,500 g	For cases < 6 years of age, OR = 1.7, 95% CI = 1.2-2.6); elevated risks observed for both ALL and AML
Kaye (1991)[11]	Birth certificates and cancer registry: ALL (n = 337)	> 3,800 g	For cases < 4 years of age, OR = 2.04 (95% CI = 1.34-3.12)
Savitz (1994)[12]	Case-control: ALL (n = 71)	> 4,000 g	Overall OR = 0.7 (95% CI = 0.2-2.3); no association for cases < 4 years of age[a]
Cnattingius (1995)[13]	Case-control: (ALL) (n = 613)	> 4,500 g	For cases < 1 year of age OR = 3.2 (95% CI = 0.5-19.7); [for ≥ 5 years of age OR = 1.7 (95% CI = 1.1-2.6)]
Cnattingius (1995)[14]	Case-control: AML (n = 98)	Not available	No association[b]
Ross (in press)[15]	Case-control: infant AML and ALL (n = 303)	> 4,000 g	OR = 2.28 (95% CI = 1.26-4.13); elevated risks observed for both AML and ALL
Yeazel (submitted)[16]	Case-control: childhood leukemia overall and by leukemia (n = 1,687)	> 4,000 g	For cases < 2 years of age at diagnosis; ALL, OR = 1.64 (95% CI = 0.97-2.76); AML, OR = 2.46 (95% CI = 1.11-5.47)

[a] Comparison of mean birthweights only.
[b] Odds ratios (OR) not provided.
[c] Comparison of twin birth order and sex of the twin pair revealed statistically significant association only for females.
[d] Statistically significant only for females ($P < 0.05$).
[e] Age at diagnosis is unclear.
[f] Statistically significant only for males ($P < 0.05$).
[g] ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia.

in Wilms' tumor tissue of patients with and without BWS.[21] This indicates that both systemic and local overproduction of growth factors can contribute to development of cancer, as was hypothesized for Wilms' tumor.[19,22]

In this paper, we suggest that growth factors may play a similar role in the development of infant leukemia. In particular, insulin-like growth factor-1 (IGF-1) plays a major role in hematopoiesis and is a major determinant of birthweight (described below). We hypothesize that IGF-1 contributes to leukemogenesis, and that this manifests in some infants as increased birthweight.

Insulin-like growth factor-1 (IGF-1)

The expression of IGF-1 has been reported in a variety of cells and tissue including liver, bone, heart, kidney, colon, and monocytes.[23] The IGF-1 gene maps to the long arm of chromosome 12; at least five exons have been identified. IGF-1 exerts its biological activity by binding to the IGF-1 receptor, which results in the phosphorylation of several signal transduction molecules.[23] In the circulation, the IGFs are bound to binding proteins, which function as regulators of IGF biologic availability; currently six IGF binding proteins (IGFBP) have been identified.[24] The major circulating IGFBP (and thus, most biologically significant) is IGFBP-3; however, in infants, IGFBP-1 and IGFBP-2 also circulate at high levels.

Growth factors and birthweight

In normal infants, many studies have demonstrated a positive correlation between IGF-1 levels in umbilical cord blood and birthweight[25-26,28-29,32,34-35,37] or fetal size,[27] with only a single contradictory study[31] (Table 2). Moreover, 40 percent lower IGF-1 levels (compared with normal infants) have been reported in small-for-gestational age newborns, whereas nearly 30 percent higher IGF-1 levels have been found in large-for-gestational age

Table 2. Selected infant cord blood parameters and correlations with birthweight and fetal size (where available)

Author (year)	Sample measured	Outcome measured	IGF-1	IGF-2	IGF-BP1	IGF-BP2	IGF-BP3
Bennett (1983)[25]	Cord blood	Birthweight	Positive (0.32)	Positive (0.46[a])	—	—	—
Gluckman (1983)[26]	Cord blood	Birthweight	Positive (0.37[a])	No correlation	—	—	—
Ashton (1985)[27]	Cord blood	Fetal weight (15-23 wks gestation)	Positive[a]	No correlation	—	—	—
Samaan (1987)[28]	Cord blood	Birthweight	Positive[a]	—	—	—	—
Lasarre (1991)[29]	Cord blood	Birthweight and fetal size	Positive[a]	No correlation	—	—	—
Salardi (1991)[30]	Fetal cord blood	Femoral length (19-37 wks gestation)	Not sensitive enough	—	—	—	—
Wang (1991)[31]	Cord blood	Birthweight	Negative correlation[a]	—	Negative correlation	—	—
Delmis (1992)[32]	Cord blood	Birthweight and fetal size	Positive correlation (0.41)[a]	—	—	—	—
Kubota (1992)[33]	Maternal plasma	Fetal size	Positive correlation (0.61)[a]	Positive correlation (0.36)	—	—	—
Fant (1993)[34]	Cord blood	Birthweight	Positive correlation (0.39)[a]	Positive correlation (0.26)	No correlation	Negative correlation (-0.26)	Positive correlation (0.48)[a]
Verhaeghe (1993)[35]	Cord blood	Birthweight	Positive correlation (0.48)[a]	Positive correlation (0.23)[a]	Negative correlation (-0.43)[a]	—	—
Reece (1994)[36]	Cord blood	Birthweight	Positive correlation	No correlation	—	—	No correlation
Simmons (1995)[37]	Cord blood	Birthweight	Positive correlation (0.43)[a]	—	—	—	—

[a] Statistically significant ($p < 0.05$).

newborns.[35] In animal studies, IGF-1 is a major determinant of fetal size, as mice lacking the IGF-1 gene are morphologically normal, but are approximately 70 percent smaller than their normal littermates.[38]

Growth factors, hematopoiesis, and leukemia

Hematopoiesis, as a mesodermal developmental process, is regulated by a number of well-characterized growth factors. These growth factors can be divided into those that regulate early and multilineage bone marrow progenitors [*e.g.* granulocytic macrophage colony stimulating factors (GM-CSF), stem cell factor (SCF), interleukin-3 (IL3)], and those that function in a lineage-restricted manner (*e.g.*, erythropoietin).[39] In addition, there is strong evidence that IGF-1 is important in blood formation including: (i) receptors for IGF-1 are found on cells of hematopoietic origin including monocytes, lymphocytes, erythrocytes, and platelets; (ii) IGF-1 plays a role in regulation of normal B-lymphocyte development; and (iii) IGF-1 stimulates erythropoiesis.[40-44] Moreover, *in vitro* studies show that IGF-1 can stimulate the growth of both myeloid and lymphoid leukemia cells.[43]

Leukemia in the infant

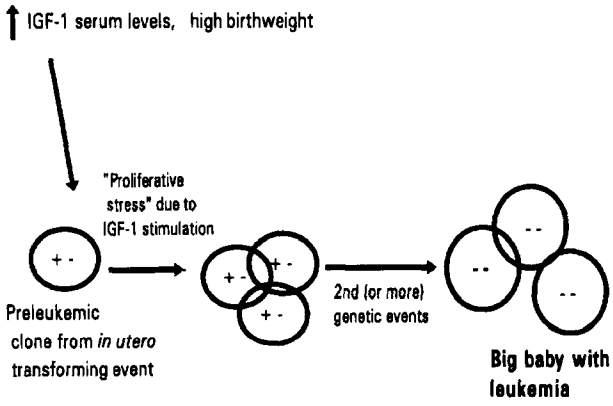
As study of the genetic basis of cancer has progressed (*e.g.*, retinoblastoma[45]), it is becoming apparent that tumorigenesis due to mutation in a single gene is probably the exception, not the rule. A more frequent process is a multi-step pathway to tumor development, with accumulation of mutations in a series of genes necessary for true malignant evolution, as has been proposed for colon cancer.[46] Evidence exists that leukemogenesis is a multi-step phenomenon also, with mutations identified in many oncogenes and tumor suppressor genes, none of which alone seem to be sufficient for malignant transformation. This means that individuals necessarily harbor a significant premalignant clone for some time before clinical diagnosis (although this has not yet been demonstrated in infants). Limpens *et al*[47] recently demonstrated that many *normal* individuals harbor the translocation, t(14;18), in their B-cells – a translocation clinically associated with follicular lymphoma. Additional evidence indicating the presence of a substantial preleukemic cell-population is the finding of cells containing t(8;21) in marrow of patients in long-term remission of leukemia who do not subsequently relapse.[48] This implies that while the truly malignant population has been eliminated by therapy, a premalignant clone remains. These findings suggest that a one- or two-hit model is not sufficient for tumorigenesis in many leukemias. Mathematical models have been produced that suggest that leukemogenesis may require the accumulation of at least four mutations or 'hits.'[49]

Molecular evidence indicates that some children who develop leukemia in the first few years of life have had at least one transforming event occur *in utero*; this is clearly true for infants diagnosed in the first few weeks of life.[50-53] In particular, nearly 80 percent of infants with leukemia present with an abnormality involving the *MLL* gene on chromosome band 11q23.[18] Taken together, these data indicate that very young children who develop leukemia likely have a population of preleukemic or leukemic cells while *in utero*.

Hypotheses

There is compelling evidence to indicate that high birthweight is associated with an increased risk of infant leukemia, and with increased circulating levels of IGF-1. Moreover, IGF-1 can stimulate the proliferation of at least a large subset of leukemia cells.[40,43-44] One hypothesis to explain the excess of leukemia in high birthweight babies may be that existing preleukemic cells are subjected to 'proliferative stress' by the higher levels of IGF-1 in larger babies (Figure 1). (Alternatively, there could be a decrease in the availability of IGF-1 binding proteins, thus allowing more free IGF-1 in the circulation.) Continued, proliferative stimulation by IGF-1 may predispose to the acquisition of additional genetic abnormalities with evolution to frank leukemia. Thus, IGF-1 could be thought of as a promoter. This hypothesis echoes Greaves' hypothesis relating to leukemia in older children,[54] which suggests that preleukemic clones acquire additional abnormalities due to proliferative stress applied to lymphocytes by delayed infection in early childhood. Protracted proliferative stimulation of preleukemic clones by hematopoietic growth factors has been implicated in the development of frank leukemia in both preclinical and clinical settings. This phenomenon has been examined most intensively with GM-CSF. Injection of immortalized, but non-leukemic (*i.e.*, preleukemic) myeloid cells

Figure 1. Potential relationships among high birthweight, insulin-like growth factor-1, and infant leukemia.



into GM-CSF transgenic mice, which overexpress GM-CSF 40-fold, leads to death from a leukemic-like illness in two to three months; however, non-transgenic littermates develop no disease.[55] In the clinic, it has been demonstrated that leukemic myeloblasts from patients with acute myeloid leukemia can be effectively recruited *in vivo* into the S-phase of the cell cycle by the exogenous administration of GM-CSF.[56] In addition, an increase in the peripheral-blood leukemic-blast count has been observed in some patients receiving GM-CSF for myeloid-lineage leukemias or preleukemic disorders.[57-59] IGF-1 may function in a similar role in infants with leukemia.

In addition to growth stimulation, IGF-1 also can function to protect hematopoietic cells from apoptosis.[60] Apoptosis, or programmed cell death, plays a central role in the normal mechanisms for the physiologic elimination of lymphocytes during lymphopoiesis, as well as in the elimination of lymphocytes that have incurred DNA damage from mutagens or irradiation.[61-62] Induction of apoptosis is also an important way in which drugs used to treat leukemia (such as steroids and DNA topoisomerase II inhibitors) kill cells.[63] Therefore, if IGF-1 is involved in the pathogenesis of infant leukemia, it also may contribute to the poor results achieved with chemotherapy treatment of these children.[64-65]

An alternative hypothesis for the excess leukemia in high birthweight babies is that the presence of preleukemic cells secreting IGF-1 leads to increased birthweight in the infant, although there are less data to support this theory. In some leukemia cases studied, IGF-1 has been shown to function as an autocrine growth factor, being produced by the leukemia cells and, in turn, stimulating the growth of those same cells.[40] The additional production of IGF-1 *in utero* produced by an autocrine loop, together with endogenous IGF-1, could have the effect of both increasing birthweight and stimulating proliferation of the preleukemic cells, increasing the opportunity for the acquisition of the additional genetic mutations for the evolution into frank leukemia.

Future investigations

Approximately 11 percent of babies weigh more than 4,000 grams at birth.[66] Using a relative risk estimate of 2.0 from the more recent epidemiologic studies,[15-16] the attributable risk of infant leukemia due to high birthweight could approach 10 percent. Technology is now available to begin to understand the biology behind the epidemiologic data. If high levels of IGF-1 produce a big baby and contribute to leukemia, we would expect to find both IGF-1 and IGF-1 receptor mRNA in the leukemic cells of the infant (as evidence of an autocrine loop), in addition to high serum levels of IGF-1. Epidemiologic and molecular biologic investigations should be able to address these important questions.

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