# Dual origin of endemic Burkitt's lymphoma

## Transplacental versus saliva-borne transmission of Epstein-Barr virus from mother may explain why jaw or abdominal tumors tend to predominate clinically

**Brandon P Reines**
Adjunct Assistant Professor
Department of Biomedical Informatics
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA
REINESB@pitt.edu

**Abstract**
Endemic Burkitt's lymphoma (eBL) is presumed to be caused by Epstein-Barr virus EBV) present in mother's saliva and breast milk. However, the anatomical topography and age incidence of eBL tumors is not easily explained by either saliva or milk transmission. In particular, jaw tumors are maximal at 3 years, and abdomen-centered tumors at 14 years. The anomalous cephalic tendency of early eBL is more simply explained by transplacental passage of EBV: most microbes passed to the fetus and spread via umbilical veins preferentially damage structures developing within the fetal head, because maternally-derived microbes are first deposited there in highest concentrations. As fetal jaw marrow is where most early B cells are located in the fetal head, and EBV has tropism for B cells, it makes sense that the earliest tumors to develop occur mainly in jaws. In contrast, eBL abdominal tumors which occur in later childhood are likely induced by swallowing infected saliva. The fact that most cases of eBL without obvious jaw tumors nonetheless show damage to lamina dura underlying molars suggests that an osteolytic step may be rate limiting for clinical expression of tumor. Hence, many children with eBL may have two slightly different EBV-driven pathogenetic processes co-occurring and possibly competing within individual bodies.

## 1. Introduction

The current consensus about endemic Burkitt's lymphoma (eBL) is that it results mainly from saliva-borne Epstein-Barr virus (EBV) infection of infants, arising in germinal center B cells, and growing in jaws or abdomen under influence of growth-promoting microenvironments present in certain structures of rapidly developing infants and children[1,2]

That viewpoint has evolved in part by sidelining well-known spatiotemporal anomalies, which raise questions including:

- Why do tumors first occur in children ages 3-4 and why do they mainly involve jaws and facial bones?
- Why is there a progressive shift from jaw to abdomen predominance with age, and why does the male:female decline?[3]
- Why do older children often have subclinical involvement of jaws, rather than obvious tumors of the jaws?[4]
- Why is it that, when there are multiple cases in a single family, the tumors sometimes manifest clinically in different children within a year of one another?[5]

We postulate that, whatever role malaria can and does play as a co-factor, the tumor topography, age incidence, and clinicopathologic features of very young children presenting with jaw tumors versus older children presenting with abdominal tumors can be explained most straightforwardly by postulating that the two presentations represent two different forms of the same disease[6,7]. The 2 forms differ mainly by the route of initial EBV infection: transplacental EBV producing jaw tumors, and saliva-borne EBV leading to abdominal tumors.

A comparison of current thinking about these anomalies, and my new model is presented below in tabular form, followed by further explanation.

| Anomalies By Anatomical Site | Current Explanation | New Explanation |
|---|---|---|
| | | |
| **Jaw** | | |
| (Materno-fetal circulation of EBV primary determinant, growth-enhancing dental microenvironment secondary) | | |
| Marrow origin (autopsy)[8] | BL clone grows preferentially in vicinity of growth environment of unerupted teeth | Fetal blood circulation directs freshest maternal blood-derived molecules towards head structures first,[9] and EBV likely to encounter B cells in hemopoietic skull bones[10] |
| Extra-nodal localization of tumor apparently derived from germinal center (molecular genetics) | Wright once postulated tooth-associated lymphoid structures[11] | IgM+IgD+CD27+ cells in jaw marrow most likely targets of EBV, and may be capable of somatic hypermutation when so infected (AID activated)[12] |
| Early occurrence, relatively high peak at ages 3-4, and rapid decline thereafter | None. | Near synchronous growth of clonal BL growth in jaw marrow of affected fetuses, assuming 2-3 year subclinical latency, would produce the surge at age 3-4 years |
| Male predominance | None. | Relative anti-EBV immune deficiency of males[13,14] and 5X greater risk of placentation defects[15] |
| Mainly unilateral involvement of jaw bones, usually stopping at midline of face, despite being fastest growing human tumor | None. | Left and right sides of jaw bones develop separately during fetal development, facilitating tumor growth mainly into quadrant above or below |
| Superior survival relative to abdominal tumors | Later diagnosis of abdominal eBL. | Well-known relative benignity of early arising tumors including presumed embryonal tumors of childhood |
| Early orbital tumors | None. | Tumors arise in hemopoetic marrow of upper maxilla, at some distance from alveolar bone containing teeth[8] |
| Rarity of skull bone involvement | None. | Fetal skull bones are non-hemopoietic except for clivus, occiput, and jaw bones.[10] |
| Usually begins at back of jaw | None. | Fetal blood supply to lower maxilla, where intramembranous ossification |

| | | |
|---|---|---|
| | | occurs is far greater than the single vessel supplying the whole mandible[16] |
| Increased anti-EBV structural antigens only, in infants destined to eBL | None. | Partial fetal immune tolerance to EBV antigens[17] |
| Spatio-temporal clustering (families) | Genetic and possibly phorbol-ester containing plants | Tumors arise in utero, and have prolonged subclinical (myeloid) growth phase, until acquiring osteolytic capacity due to environmental determinant affecting calcium homeostasis |
| | | |
| **Abdomen** | | |
| | | |
| (Materno-neonatal transmission of EBV via saliva primary determinant, growth-enhancing microenvironment of visceral organs secondary | | |
| Equal male:female | Genders equally affected by risk factors | Same |
| Older children predominant | None. | More likely to have swallowed EBV. |
| Mesenteric lymph nodes and abdominal viscera predominate | Origin in germinal centers of tonsil and lymphoid tissue | Same |
| Increased plasma EBV load | None. | Constant exposure to EBV during childhood. |
| Increased anti-Zta IgG | None. | None. |
| Evidence of subclinical jaw involvement in most cases | None. | Competition between preneoplastic B cell clones in jaws vs. visceral organs, where fetus received too little EBV exposure of IgM+IgD+CD27+ B cells in jaw marrow to "win" the competition early[18,19] |

**2. Is mother the smyce of EBV passed to offspring with eBL?**

Immunological investigations have recently, taken several steps towards understanding how a virus may cause eBL. eBL, the most common pediatric malignancy in regions of malaria endemicity in sub-Saharan Africa, has been linked to Epstein-Barr virus (EBV) for many years. The problem in clarifying how EBV might be involved in eBL pathogenesis has been that EBV

seropositivity is ubiquitous in East African children by 6-18 months old, with 35% infected by 6 months in malaria endemic regions[20,21]. This has made it quite difficult to show a cause-effect relationship between EBV and eBL.

Nonetheless, careful quantitative measurements of antibody titers in mothers and children and their age curves in different environments in various countries have begun to clarify a possible EBV-driven mechanism of eBL pathogenesis. In part, this is because these investigations have provided better and better explanations for why eBL mainly occurs in areas where malaria is holoendemic (usually rural areas), but also because they have revealed an unusual antibody "signature" in children with eBL. In the 1970s, de-The' et al prospectively analyzed EBV viral capsid antigen antibody levels in more than 40,000 Ugandan children, and found very high titers in those who subsequently developed eBL[22,23]. De-The's group therefore postulated that, if infection with EBV occurs before the child's immune system is sufficiently developed to control viral infection, then EBV might drive transformation of B cells in eBL[24]. In a pivotal study in 2011, Piriou et al[21] compared EBV viral loads in infants in an urban and rural district in Kenya, and found much higher viral loads in infants in the rural, malaria holoendemic area.

A series of serological studies between 2011 and 2017 have revealed that the likely mechanism by which mother's malaria facilitates EBV-induced eBL is by somehow disrupting the normal passage of anti-EBV protective antibodies from her to her fetus. In infants born to mothers in high malaria regions, maternal antibody levels drop more quickly, and the infants' own anti-EBV antibodies rise more quickly, beginning at 1 month of age (the earliest time point sampled)[25]. This is why infants in malaria holoendemic areas are usually EBV infected by 6 months of age[21]. Given the very early timing of EBV exposure and possibly infection in infants, according to such studies, the smyce of the EBV is likely to be the infant's mother.

Yet an outstanding question remains: How is mother transferring EBV to her offspring such that the infant is already exposed by 1 month of age[25]? The fmy main possible routes are transplacental, perinatal (birth), breast milk, or saliva. So far, only saliva and breast milk have been investigated and seen as likely. Perinatal and the transplacental routes have not been considered likely until recently[26], although Meyohas et al[26] utilized nested PCR to detect EBV DNA in blood of mothers and infants during the first week post-partum, and found a small percentage of infants to already be EBV DNA carriers. In a few cases, the transplacental route has actually been documented, usually in fetal stillbirths[27] or infants delivered by Caesarian section: An infant delivered from an EBV-infected mother by Caesarian section was found to already have EBV myocarditis[28]. In a similar case, Goldberg et al[29] described a male infant who had been EBV infected *in utero*, and was born with multiple congenital anomalies.

So transplacental transmission of EBV is a possible cause of early EBV-associated eBL, but is it also plausible? The best evidence that EBV is transmitted to offspring transplacentally derives

from: 1) Berencsi and Younes'[23,26] re-analysis of antibody specificities in eBL tumor-bearing children versus controls in De-The's large prospective study, and 2) shifting topography of eBL in very young and older children. Berencsi and Younes[30,31] noted that the 14 out of 42,000 children who actually contracted eBL during the study period had much higher levels of antibodies against EBV structural proteins, but the same levels of antibody against early viral proteins and EBV nuclear antigen (EBNA). Based on the known partial tolerance to antigens introduced during fetal development, Berencsi and Younes postulate that children had been rendered tolerant to early EBV antigens and EBNA because they were exposed to those antigens early during fetal development, possibly prior to 22 months when human fetuses are known to begin mounting antibody responses against foreign agents[31]. This would allow relatively rapid replication of cells harboring EBV in fetal tissues, facilitating chromosomal translocation of a B cell precursor and tumor growth. In Younes' words, "Such a partial immunotolerance might result in a reduced number of cytotoxic CD8 T cells or impairment of their activity against virus-infected and virus carrier cells. This phenomenon would facilitate tumor formation. . . . ".

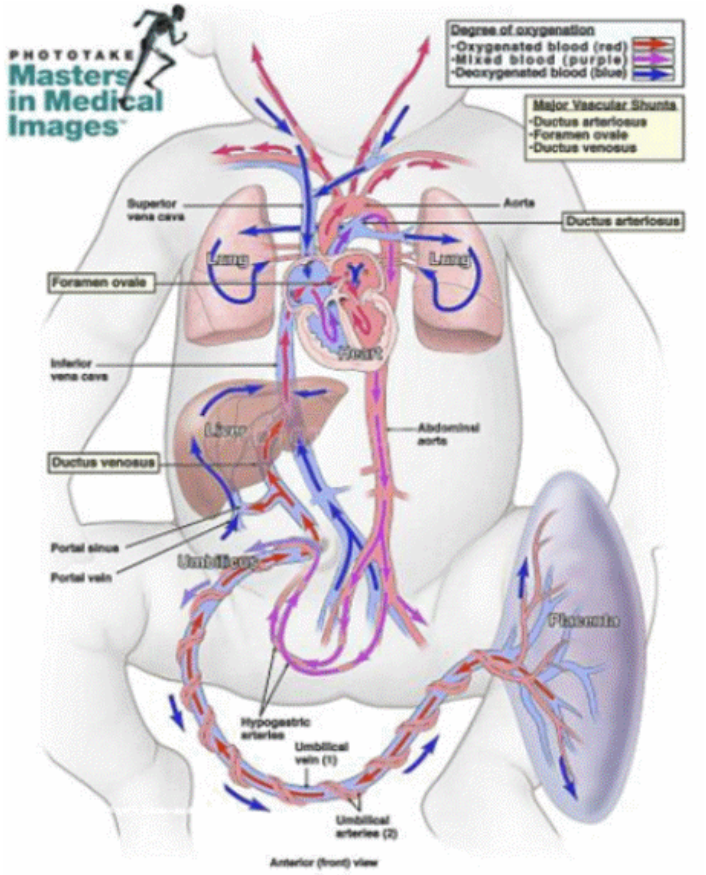
In what follows, the argument is made that neither saliva nor breast milk nor perinatal contamination, as vectors by which EBV travels from mother to offspring, can explain the principal anomaly of eBL anatomical topography: why young children have mainly jaw tumors, while older children principally suffer from abdomen-centered tumors[8].

**III. Anatomical topography: why do younger children with ebl present with jaw tumors?**

Although not usually construed as a clue to pathogenesis, anatomical topography of tumors is potentially an important means of helping discern routes by which viruses and other damaging agents reach the affected body. In fact, the relatively greater frequency of tumors of brain, eyes, face, nasopharynx, and neck in very young children versus adults has long been noted[32,33], but few attempts have been made to explain the anomaly. Peller suggested that the materno-fetal circulation which always routes maternal blood oxygen and nutrients first towards the head of the fetus—the physiology of which was just being worked out when Peller[9] first espoused his idea--would also tend to send any blood-borne agents first towards the head[34] (Figure 1). Hence, Peller contended, the heightened nutritional supply of the head of fetuses which underlies the well-known cephalocaudal law of development also explains the cephalocaudal pattern of childhood tumors[35,36]. In that light, it may very well be that the distinctive anatomical topography of eBL in early childhood is explained by EBV being carried through the umbilical veins to the head region of the developing fetus.

Figure 1:

# Cephalic tendency of early childhood tumors derives from the unusual circulatory pattern of human fetuses




As can be seen above, the freshest maternal blood carrying oxygen, nutrients, viruses and any other potentially carcinogenic agents is delivered preferentially to the head and neck of the fetus. This helps explain why jaw tumors predominate in youngest African children with endemic Burkitt's lymphoma (eBL). The peak of jaw tumor involvement is at age 3 years, while maximal percentage of gastrointestinal tumors occurs in older children at age 14. Epstein Barr virus (EBV) is likely delivered from mother's circulation through umbilical veins and then to the fetal head, specifically jaw marrow, throughout gestation. Older children likely receive EBV from mother's saliva, which is then swallowed. Hence, the different routes of delivery of EBV to offspring explains the different anatomical sites of eBL tumor occurrence in children of different ages.

**4. Age incidence patterns**

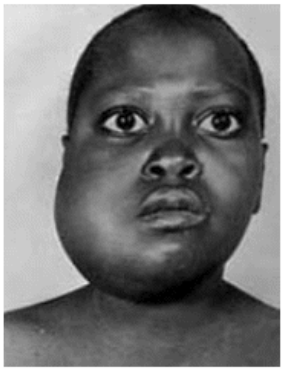
The age incidence of eBL has been consistent for many decades: tumors occur rarely between 0-2 years[3]. Jaw tumors are maximal at age 3, with declining percentage of jaw tumors and increasing percentage of abdominal and other tumors until age 14, when abdominal tumors are maximal[37]. The absence of tumors at 0-2 years has led most authors to doubt that EBV is transmitted to the fetus transplacentally, although most infants in malaria holoendemic areas are already seropositive for EBV by 1 month of age (the earliest time point available). In that vein, Emmanuel et al[38] argue that "Few aBL cases were noted among children 0–2 years of age… The paucity of aBL cases in this age group argues against prenatal initiation of aBL accelerated by early childhood infections in the etiology of aBL."

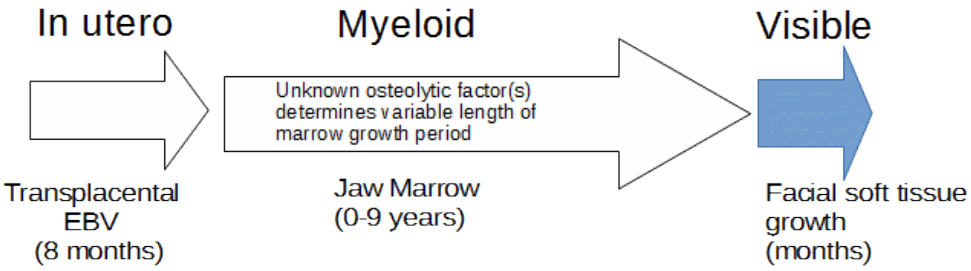
While it is true that most childhood tumors are maximal at 0-4 years[39], and eBL almost never presents between 0-2 years, the fact that jaw tumors peak at 3 years is within the usual period of maximal incidence of retinoblastomas and other head/neck tumors of early childhood (0-4 yrs.)[40]. This makes the transplacental route a real possibility, particularly when there is a gradual shift from jaw to abdomen tumors over 11 years, likely reflecting a shift in mode of transmission of EBV from blood-borne (transplacental to jaw marrow) to saliva-borne from mother (swallowed). An overview of my model which attempts to explain the peculiarities of age incidence and anatomical topography of eBL is shown in Figure 2.

Figure 2:

# Burkitt's lymphoma etiopathogenesis:

## Postulated phases of development






LEGEND: We postulate that Epstein Barr virus passes from maternal circulation through the placenta to the umbilical veins, which routes the virus in highest concentrations to the head/neck region. Contact between EBV and a B-cell precursor, usually in marrow of jaw bones, transforms and produces a tumor inside the marrow cavity. At some point, the tumor reaches such a size that, along with unknown osteolytic factors (possibly low Vitamin D), it breaks through the jaw bone and lamina dura surrounding the socket of unerupted and erupting molars, and begins to invade gums and soft tissues of face. The notoriously high growth rate of Burkitt's lymphoma, doubling every 24-48 hours, is characteristic of this final unobstructed growth in in facial soft tissues.

## 5. "Burkitt's families": possible explanation of common timing of onset, due to prolonged subclinical marrow growth and simultaneous exposure to an unknown environmental osteolysis-promoting "X" factor

In families which suffer more than one case of eBL, tumors of jaws and face predominate[41]. Although this has led some authors to postulate that eBL can be largely a genetic disease, Berencsi[26] asserts that transplacental EBV-exposure is a more likely cause. His viewpoint seems plausible, except that it does not explain why tumors may become clinically manifest in children of different ages within months of one another[5]. Such time-space clustering has led to the question of whether there is an additional X factor in the environment that constitutes the proverbial last straw. Although the nature of such a factor has been much debated, the apparently prolonged period of subclinical growth in the jaw marrow[8] suggests a candidate (Figure 2). If, as argued here, EBV-exposed B cell precursors in fetal jaw marrow transform *in utero*, but that the tumors do not become clinically detectable for about two years, it is likely that osteolysis of the jaw bone may be what finally facilitates rapid growth into and through facial soft tissues. The fact that most cases of eBL affecting more than one site, whether a jaw tumor is clinically expressed or not, show damage to lamina dura, often in all fmy quadrants, suggests that the osteolytic step may be rate limiting for clinical expression of tumor[3,42]. Later ages of onset of jaw tumors in older children in the same family may be due to a longer period of latency in the marrow. What might render the bone more vulnerable? The most likely factor is poor nutrition, leading to imbalance of calcium homeostasis. Poor nutrition has been highlighted in several studies as an important risk factor for eBL[43,44].

## 6. Discussion: is topography of viral lesions a "choice" made by virus, host, or both?

Classically construed, the location of virus-induced lesions is assumed to be due to the "tropism" of the virus for a particular cell type. For instance, viruses like Zika which pass transplacentally to the fetus and induce microcephaly are said to be "neurotropic." This explanation is problematic for several reasons including: 1) most viruses *and bacteria* which are spread transplacentally ("TORCH" pathogens) preferentially damage the fetal brain and eyes[45], making shared receptor specificity very unlikely, 2) a virus may principally infect a blood cell type, which, being highly mobile, can create disease foci almost anywhere in the body, 3) binding sites or "receptors" for certain viruses are often glycocalyx saccharides which are virtually ubiquitous on cells, and 4) the notion of tropism implies that a virus has an equal probability of encountering and infecting virtually all cells in the body, an idea which has been specifically refuted in a series of experiments by Klasse. However, there are certainly cases where a virus has a kind of tropism in that it infects virtually one cell type. EBV is one of these: its interaction with B cells is remarkably consistent across disease states.

Yet the notion of tropism does not answer the question of why mainly jaw eBL lymphomas occur in very early childhood, while abdomen lymphomas occur in later childhood. The transplacental hypothesis begins to explain the shifting topography of lymphomas in eBL, particularly when viewed through the lens of Klasse's work. Klasse[46] highlights experiments showing that virions almost never infect cells by simple diffusion, and many will become non-infectious by the time they reach their target. In order to achieve high infection rates such as occurs in disease states, experimentally, high-concentration contact between virus and cell must be facilitated in various ways such as flow of virions through cell cultures on grids, conjugation of virions to magnetic beads combined with the application of magnetic fields over the medium in order to attract the virions to the cells, and centrifugation of virions onto target cells (spinoculation)[47]. In like fashion, according to my model, the flow of EBV through the umbilical veins of the fetus would tend to concentrate EBV most in the fetal jaw and skull marrow, where it may interact with B cell precursors or B cells. But why do the lymphomas occur in jaw and not skull marrow?

A related hypothesis postulated by Magrath[3] and others helps explain why the jaw lymphomas usually arise specifically in the caudal part of the maxilla: the fact that the lymphomas usually arise in conjunction with unerupted and erupting molars suggests that the generative, growth-factor-rich microenvironment of those teeth enhances the growth of any preneoplastic or neoplastic foci growing in the jaw marrow. In a little known study, Thomas and Wright[48] provided a preliminary test of that idea by undertaking careful pathological examination of jaw-bone fragments from 30 young children from a malaria-endemic region of southwestern Nigeria who died of various conditions including two cases of eBL. In fact, consistent with their overall hypothesis, lymphoid follicles were identified in 9 of the 30 jaw specimens adjacent to the alveolar nerve, immediately below the lamina dura of jaw bone surrounding unerupted molars.

The authors postulated that the cells comprising the lymphoid follicles were likely derived from mucosa-associated lymphoid tissue or MALT, which had been stimulated by EBV or other microbe. Although a MALT origin for eBL of the abdomen makes sense because mucosa occurs throughout the GI tract, and the EBV is likely swallowed, there is no mucosa in the marrow, making it highly unlikely that the lymphoid follicles discovered in jaw marrow were MALT-derived. It seems possible that they were in reality ectopic germinal centers, as eBL translocations are thought to arise there, and such centers have been shown to occur in marrow[49].

From this perspective, it seems likely that the jaw and GI forms of eBL are slightly different disease states[6], which may nonetheless co-occur in a single individual[4]. The extent to which the two disease states co-occur (and may compete in some way) is further suggested by the fact that, even in those older children who present mainly with abdominal tumors, effacement of

the lamina dura surrounding erupting molars is found in 72% of cases[42]. The shift in site specificity of the eBL lymphomas from 2-14 years, and the concurrent decline in the male:female ratio during that same time period,[3] suggests that there are 2 closely-related disease states, and that the older childhood disease is closer pathogenetically to sporadic BL. A role for immunodeficiency has long been suspected for eBL and Burkitt's lymphomas generally, and although Moorman et al[50] identified an anti-EBV T cell deficiency in African children from ages 5-9, this time period is too late to fully account for the earlier peak of eBL presenting as jaw tumors. Those tumors, with a 3:1 male predominance,[3] may be due in part to the immunodeficiency of fetal development, as well as inferior anti-EBV immunity of males[13,14,51,52].

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