SEVERE EBV INFECTION IN PRIMARY IMMUNODEFICIENCY AND THE NORMAL HOST

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Abstract

EBV infection is ubiquitous in humans, but the majority of infections have an asymptomatic or self-limiting clinical course. Rarely, individuals may develop a pathological EBV infection with a variety of life threatening complications (including haemophagocytosis and malignancy) and others develop asymptomatic chronic EBV viraemia. Although an impaired ability to control EBV infection has long been recognised as a hallmark of severe T-cell immunodeficiency, the advent of next generation sequencing has identified a series of Primary Immunodeficiencies in which EBV-related pathology is the dominant feature. Chronic active EBV infection is defined as chronic EBV viraemia associated with systemic lymphoproliferative disease, in the absence of immunodeficiency. Descriptions of larger cohorts of patients with chronic active EBV in recent years have significantly advanced our understanding of this clinical syndrome. In this review we summarise the current understanding of the pathophysiology and natural history of these diseases and clinical syndromes, and discuss approaches to the investigation and treatment of severe or atypical EBV infection.

Introduction

Epstein Barr Virus is a γ-herpesvirus characterised by restricted infectious specificity to humans, and latent infection in B lymphocytes. EBV is naturally transmitted through saliva (Gerber et al. 1972). Primary infection with EBV typically occurs in childhood as a symptomless or mild infection, with early infection seen in a higher proportion of the population of low income compared to high income countries (Cohen 2000; Pariente et al. 2007; Hjalgrim, Friborg, and Melbye 2007)(e.g. 58.9% of Zambian infants aged 12 months are EBV seropositive (Minhas et al. 2010) compared to 7.1% of infants in a Swedish infants (Hesla et al. 2013)). By age 30, >95% of adults in Europe and North America are seropositive (Cohen 2000; Pariente et al. 2007; Pembrey et al. 2013). Primary EBV infection in adolescence or adulthood leads to a 25-70% risk of developing a symptomatic EBV infection, known as infectious mononucleosis (IM) (Higgins et al. 2007; McAulay et al. 2007). This is characterised by pharyngitis, benign lymphoproliferation, fever and malaise, and symptoms lasts up to 6 weeks duration in the majority of patients.

Following primary infection, EBV persists within resting memory B cells (Miyashita et al. 1997) with low immunogenicity (Babcock, Hochberg, and Thorley-Lawson 2000), allowing a life-long infection to be established, which the immune system cannot clear.

EBV Life cycle

EBV has a biphasic life cycle, divided into lytic and latent gene expression programmes (Tsurumi, Fujita, and Kudoh 2005)(figure 1). The lytic gene expression programmes allow EBV to productively infect new cells and new hosts, while establishment of latency is vital to allow life-long persistence of the virus within infected cells, through a highly restricted gene expression profile in order to avoid immune surveillance (Young, Arrand, and Murray 2007).

The first cells thought to be infected by EBV during primary infection are oral epithelial cells and naïve B cells (Balfour et al. 2013). During the lytic cycle, EBV infection is followed by the induction of two immediate early proteins (BRLF1 and BZLF1) which act as transcriptional activators for a wide range of proteins and viral RNAs involved in viral DNA replication or viral structural proteins. True latency (type 0), where cells express no EBV protein or RNA, but retain senescent episomal EBV DNA, is subsequently established in the resting B memory pool. Although this transition to latency is not fully understood, a model proposing EBV exploitation of the physiological B-cell differentiation pathway is helpful when considering the pathological states following EBV infection (Thorley-Lawson et al. 2013)). In this, infected naïve B cells enter a proliferative phase during which they express the full range of latent EBV proteins and viral RNAs (latency type 3, equivalent of *in vitro* derived B lymphoblastoid cell lines). A proportion of these cells differentiate further into latency type 2 within the oropharyngeal germinal centres in response to EBV-specific T follicular helper cells, resulting in restriction of EBV protein expression to EBV nuclear antigen (EBNA) 1, latent membrane protein (LMP) 1 and 2 proteins only. Further differentiation results in the release of latency type 0 resting B memory cells into the circulation. Sporadically, as these cells recirculate through the oropharynx, a proportion switch from the immunologically silent latent infection, to the productive lytic cycle.

The virus is shed at particularly high levels from four-six weeks after initial infection (Dunmire et al. 2015), reducing as the infected individual convalesces. Low-level shedding of EBV in saliva (and the possibility of infecting new hosts) continues sporadically for life (Hadinoto et al. 2009), as cycles of lytic reactivation within B-cells and oropharyngeal epithelial cells are interrupted by immunological control, leading to a return to latent infection (Taylor et al. 2015).

From epidemiological studies and *in vitro* work, a number of factors have been identified which may drive the change from a latent to a lytic gene expression profile in cells infected with EBV (Kenney 2007). In latently infected individuals it has been shown that stress (e.g. caused by sleep deprivation) leads to increased EBV genome production (Uchakin et al. 2011; Mehta et al. 2000) and EBV lytic transcription factor BZLF1 may be induced by glucocorticoids (Yang et al. 2010) demonstrating a link between the host environment and permissivity of viral reactivation. Suppression of T-cell immunity (for example after organ transplantation) is also strongly associated with EBV reactivation (Hiwarkar et al. 2013), as is concurrent infection with some other pathogens, such as Group A *Streptococcus* (Ueda et al. 2014) and malaria (*Plasmodium falciparum*) (Moormann et al. 2005; Rochford, Cannon, and Moormann 2005; Rickinson 2014).

Immune Response to EBV infection

Primary EBV infection in the immunocompetent host leads to distinct antibody profiles. The EBV proteins expressed during lytic infection, such as Viral Capsid Antigen (VCA) and Immediate Early Antigen (EA), are often highly immunogenic with antibodies to VCA detectable up to a week before the onset of IM symptoms. Antibodies responses to latent proteins are delayed, with EBNA2 specific IgG appearing at the height of symptoms, and the anti-EBNA1 IgG response developing from 3 months post-infection. The hallmark of primary EBV infection is detectable IgM and rising IgG VCA antibody responses, in the absence of an EBNA1 IgG response (Taylor et al. 2015). In a study of individuals who had recently experienced IM, 88% of individuals were positive for VCA-IgM, 100% were positive for VCA-IgG, and 96% were positive for EBNA1-IgG (Balfour et al. 2013).

Studies of individuals in the early stages of EBV seroconversion show an expansion in peripheral Natural Killer (NK) cells at the point of symptom onset, 4-6 weeks after initial infection (Balfour et al. 2013). Although NK-cell numbers correlate with virus load in the peripheral blood, they demonstrate little evidence of increased activation, as measured by levels of granzyme B. CD8+ T-cell expansion follows the same pattern with a dramatic proliferation of lytic antigen specific CD8+ T-cells during IM, and a much smaller response to latent antigens. Onset of symptoms correlates much more closely with this CD8+ cell expansion, than with EBV viral load, supporting a model of IM as an immunopathic disease (Balfour et al. 2013). During asymtpomatic EBV infection, there is similar development of EBV-specific CD8+ve cells, with clonal dominance of the CD8+ repertoire, however the total CD8+ T-cell counts remain within the normal range, suggesting activated CD8+ T-cell over-proliferation is associated with symptomatic disease(Jayasooriya et al. 2015). CD4+ T-cell expansion also occurs during IM, although this is less dramatic than the CD8+ response. By contrast to CD8+ cells, the CD4+ response is predominantly towards latent EBV antigens and demonstrates less clonal immunodominance, with a wider distribution of epitope responses. A detailed review the immune response to EBV infection can be found elsewhere (Taylor et al. 2015).

Pathological Responses to EBV infection

Although the majority of individuals infected with EBV have an asymptomatic or self-limiting clinical course, there is a broad range of pathological responses to infection, encompassing prolonged fever and lymphoproliferation (severe IM), haemophagocytic lymphohistiocytsosis, autoimmunity and malignancy. These states arise from unregulated cytotoxic and inflammatory responses to EBV infected B-cells, impaired T-cell or NK-cell immune surveillance of EBV infected cells, EBV infection in aberrant (non-B) cells or as yet undefined mechanisms. Each of these pathological mechanisms can be in seen in immunodeficient patients (primary and secondary) or apparently normal hosts. Our understanding of the interaction between EBV and the host response to infection is improving, but we are far from truly appreciating the complexities of genetically determined susceptibility to pathological EBV-associated states.

Haemophagocytic lymphohistiocytosis (HLH)

HLH is a severe, life-threatening immunodysregulatory disorder resulting from the uncontrolled activation and proliferation of T-cells and macrophages, which causes excessive production of cytokines, hyperinflammation and tissue damage. It is classified as either primary HLH, when a family history of the disorder or identified genetic defect is present, or secondary HLH which can be associated with infection, rheumatological disorders (often termed macrophage activation syndrome) or malignancy. It is debatable whether all patients with ‘secondary HLH’ also have a genetic susceptibility to develop a hyperinflammatory response to a trigger, and indeed evidence in support of this theory is emerging (Zhang et al. 2008; Weaver and Behrens 2014; Zhang et al. 2014). Increasingly, HLH is also recognised as complication of more “classical” primary immunuodeficiencies (PIDs) (Bode et al. 2015). The causes of primary HLH and the investigations required for their diagnosis are summarised in Table 1.

In the normal setting, cytotoxic T lymphocytes (CTLs) and NK-cells, once in contact with a virally infected cell, respond by forming an immunological synapse with the target cell followed by granule-mediated cytotoxicity. This not only clears the virally infected cells but regulates the inflammatory response by removing antigenic stimulus. All forms of familial HLH result from impaired granule-dependent cytotoxicity due to abnormalities in the trafficking, docking and exocytosis of granules, or in perforin function. Perforin is a key protein in this process, creating pores in the target cell membrane to allow entry of granzymes leading to target cell death (Voskoboinik, Smyth, and Trapani 2006). Without target cell death, antigen presenting cells continue to stimulate CTLs, leading to the ongoing production of cytokines, in particular IFN-γ, which further drives macrophage activation and histiocytic transformation (Jordan et al. 2004). Macrophages and activated T cells infiltrate tissues secreting high levels of inflammatory cytokines, chemokines and other substances that lead to the symptoms of HLH. Cytopenias result from both haemophagocytosis and high levels of TNF-α, IFN-γ and ferritin which suppresses haematopoiesis (Larroche and Mouthon 2004). Much of our understanding HLH comes from the immunopathology of familial cytotoxicity defect syndromes, however the pathogenesis of other forms of primary and secondary HLH is likely to involve the same mechanisms.

Regardless of the underlying cause, the clinical features of HLH are similar, although patients with primary HLH tend to present in infancy (Janka 2007; Cetica et al. 2016). Clinical manifestations include prolonged fever, hepatosplenomegaly, hepatitis, cytopenias, coagulopathy, rashes and neurological symptoms. The Histiocyte Society has developed diagnostic criteria for HLH, based on both clinical and laboratory findings (Table 2), to help guide the initiation of therapy.

Standard of care treatment remains established, highly immunosuppressive, chemotherapeutic protocols (HLH 94 and HLH 2004 (Henter et al. 2007; Henter et al. 2002)) combining etoposide (VP-16) with steroid therapy, +/- ciclosporin, with the aim of removing and controlling destructive immune cells and suppressing inflammation. If neurological features are present intrathecal methotrexate should be included. Supportive care is vitally important as is treating suspected triggers, including EBV infection, which may require multiple courses of Rituximab. Published data suggests that 71% of patient achieve remission on the HLH 94 protocol but 29% of patients die before reaching transplant and 5-year survival post-HSCT is 54% (Trottestam et al. 2011). Following induction therapy patients with primary HLH should proceed urgently to Haematopoietic Stem Cell transplant (HSCT). Long term management of secondary/undefined HLH is more difficult; however our practice is to progress to HSCT in patients with refractory or relapsing HLH even in the absence of a defined genetic aetiology.

It is critical to achieve remission prior to HSCT as the outcome in patients with active HLH is significantly worse. The introduction of reduced intensity conditioning (RIC) regimes has improved the outlook for patients with primary HLH affording 3-year survival rates of 92% compared to 43% when myeloablative conditioning is used (Marsh, Vaughn, et al. 2010). Results still remain disease specific, with certain inherited disorders associated with reduced survival post-HSCT as highlighted below. Detailed reviews of treatment strategies including salvage therapy and the increasing use of anti-thymocyte globulin (ATG) and monoclonal antibodies in this context are available (Jordan et al. 2011; Mahlaoui et al. 2007).

Chronic Active EBV (CAEBV)

Chronic Active EBV (CAEBV) was originally used to describe patients with chronic or recurrent infectious mononucleosis (Straus 1988). It is now defined as EBV related illness lasting greater than 3 months, associated with systemic EBV positive lymphoproliferative disease (LPD) (with elevated EBV DNA/RNA in affected tissues), and high level EBV viraemia or increased anti-VCA IgG titre, in the absence of defined primary or secondary immunodeficiency (Cohen et al. 2011; Kimura et al. 2005; Kimura et al. 2001; Kimura et al. 2012; Okano et al. 2005) (see table 2). CAEBV has been most commonly described in East Asia where the proliferating cells are usually T or NK-cells (Kimura et al. 2012). This clinically heterozygous condition has overlap with two cutaneous syndromes – Hydroa Vacciniforme-like lymphoma (a recurrent vesiculopapular eruption usually caused by an EBV infected γδT-cell infiltration) and mosquito bite sensitivity associated with EBV positive lymphoproliferation (usually NK-cells) (Kimura, Kawada, and Ito 2013) (see figure 2). In Western countries, CAEBV is rarer but usually associated with B cell proliferation (Cohen et al. 2011). In all of these conditions the lymphocyte, and EBV clonality may be monoclonal, oligoclonal or polyclonal.

Clinically CAEBV patients demonstrate an aggressive course with complications ranging from progression to HLH and/or lymphoma, disseminated intravascular coagulopathy, coronary artery aneurysms, CNS disease, myocarditis, pneumonitis and gastrointestinal perforation (Kimura et al. 2001; Kimura et al. 2012; Cohen et al. 2011). In the largest series of 108 patients with EBV-associated T/NK-cell LPD, survival at a median follow up of 46 months was 44%. Patients with isolated cutaneous disease appear to have a better prognosis and those with CD4+ T cells as the EBV infected proliferative cell, do worse (Kimura et al. 2012). Complications and prognosis for CAEBV with B-cell lymphoproliferation in the US seems to be similar, although interestingly 42% of these patients developed progressive hypogammaglobulinaemia and B-cell lymphopenia (even in the absences of rituximab therapy) (Cohen et al. 2011)

CAEBV patients have significantly higher loads of EBV DNA in mononuclear cells compared to patients with IM (Xing et al. 2013). Characteristically, patients have very high IgG antibody titres to EBV early antigen (EA) and VCA, but lack an IgG response to EBNA1 (Kimura et al. 2003), however, this pattern may be absent in up to 50% of patients and is therefore of limited diagnostic value. The pathophysiology of CAEBV is poorly understood. Despite the above antibody pattern being suggestive of a predominance of EBV lytic cycle infection, T and NK-cells demonstrate EBV infection in type 2 latency (Kimura et al. 2005). CAEBV patients have a hyperinflammatory state with cytokine profiles (raised IL-1β, IL10, IFNγ) similar to patients with familial HLH (Ohga et al. 2001), suggesting an equivalent pathophysiology, with impaired removal of EBV infected T/NK-cells driving a local inflammatory response in infiltrated tissues, and a resultant pro-oncogenic and haemophagocytic environment (Rickinson 2014).

EBV-positive systemic T-cell lymphoproliferative disease (STLPD) is a lymphoma of αβ T-cells with an activated phenotype. It usually develops following acute EBV infection, but can also arise as a malignant progression from CAEBV (Kimura, Kawada, and Ito 2013). By definition this is a systemic illness caused by clonal proliferation of EBV infected T cells (Quintanilla-Martinez, Kimura, and Jaffe 2008). It almost invariably is associated with haemophagocytosis, and as the proliferating cells rarely show evidence of atypica the differentiation from HLH or CAEBV is often difficult. It is perhaps best thought of as the common neoplastic path of lymphoid proliferation in both HLH and CAEBV (Hong et al. 2013). Interestingly the presence of monoclonality in HLH does not appear to impact on outcome (Ahn et al. 2010).

Treatment of CAEBV and STLPD remains unsatisfactory, with most patients treated according to their predominant clinical syndrome (HLH or lymphoma). Rituximab, antiviral and chemotherapeutic drugs and may have a role in stabilising early disease in occasional patients, but any clinical benefit doesn't appear to be sustained. Results of early HSCT with RIC are encouraging, suggesting that conservative therapy should be reserved for patients with isolated cutaneous disease and easily controlled inflammation (Kimura et al. 2012; Cohen et al. 2011; Kawa et al. 2011).

EBV driven malignancy and autoimmunity

EBV-driven malignancy is seen in both immunocompentent and immunodeficient patients, with malignant transformation of lymphoid cells (T, B and NK-cells), and non-haematopoeitic cells (Figure 2). Pathophysiology is multifactorial with the following being key pathogenic processes; (1) loss of immune surveillance / EBV-mediate immune evasion, (2) EBV infection induced growth factor and cytokine production, (3) EBV oncogene expression (particularly LMP1 and LMP2A) and (4) genetic / epigenetic alteration of the host genome. The relative importance of each of these mechanisms varies for each individual malignancy (Murata, Sato, and Kimura 2014; Rickinson 2014; Taylor et al. 2015).

EBV has also been implicated in the pathophysiology of autoimmunity, best characterised by associations with multiple sclerosis and systemic lupus erythematosis (Taylor et al. 2015; Thacker, Mirzaei, and Ascherio 2006)

Common human genetic variation in EBV infection and immunity

Susceptibility to EBV infection and disease may be described as a spectrum. At one end lie rare monogenic mutations with large effects (Houldcroft and Kellam 2015), and at the other end are common polymorphisms with small effects, leading to subtle changes in risk of, and response to, infection. In the middle is a less well defined category of low-frequency variants which are associated with disease phenotypes, but are also found in apparently healthy members of the population (Manso et al. 2014), with no clear biological impact on gene function.

Genome-wide association studies (GWAS) are beginning to impact on our understanding of the common genetic variants underlying population response to EBV infection. Individuals vary in their antibody titres to EBNAs, and the heritability and common genetic variants underlying this variability have been probed in a number of recent studies. A series of GWAS have identified single nucleotide polymorphisms (SNPs) within HLA class II genes as important for antibody response to EBV, specifically IgG antibodies to EBNA-1 (Hammer et al. 2015; Pedergnana et al. 2014; Rubicz et al. 2013).

Candidate gene studies have also associated anti-VCA IgA and IgG titres to variants in a number of genes (Houldcroft and Kellam, 2015), but these variants have yet to be validated by the more agnostic GWAS approach. Many candidate gene studies have focused on functional variants within the promoter region of interleukin-10 (IL10) (reviewed in (Houldcroft and Kellam 2015), in part because EBV encodes a viral homolog of IL10 (BCRF1) (Moore et al. 1990), but also because of the many roles IL10 plays in EBV infection, (regulatory T cell response to EBV (Marshall, Vickers, and Barker 2003), promotion of latent infected B cell survival (Incrocci, McCormack, and Swanson-Mungerson 2013)).

(Houldcroft and Kellam 2015)Candidate gene studies have also suggested variants within the HLA class 1 system as being important for susceptibility to EBV infection (Durovic et al. 2013), and risk of symptomatic infection (IM versus silent seroconversion) (McAulay et al. 2007). Finding the common genetic variants underpinning infectious mononucleosis is an achievable goal for approaches such as GWAS, as studies of IM risk in twins (Hwang et al. 2012) demonstrate that monozygotic twins have twice the relative risk of concordance for symptomatic IM compared to dizygotic twins. Similarly, first degree relatives (Rostgaard, Wohlfahrt, and Hjalgrim 2014) show a heritable component of IM risk, based on studies of individuals hospitalised with severe IM, with rate ratios of IM increasing as genetic relatedness increased.

EBV genome variation and its role in disease

In addition to genetic susceptibility of the host, it is possible that genetic variability in the EBV genome may play a role in the pathogenesis of severe EBV infection.

The genome of EBV is approximately 184kb long, formed of linear double-stranded DNA. Following primary infection, EBV persists in B cells as an episome and does not normally integrate into the human genome, although aberrant EBV integration events are seen in some EBV-positive cancers Raab-Traub 2007). Genetically and phenotypically, there are two types of EBV (1 and 2) and these types have different geographic distributions. EBV type 1 is most prevalent and occurs worldwide, while EBV type 2 seropositivity shows widespread geographic variation and is reported in 20-25% of EBV seropositive individuals in parts of Africa and Melanesia (Young et al. 1987). Co-infection with EBV type 1 and EBV type 2 is infrequently detected (Chang et al. 2009). Recombinant strains between EBV type 1 and EBV type 2 have been also reported (Burrows et al. 1996).

EBV type 2 transforms B cells more poorly than EBV type 1, and there is some *in vivo* evidence that type 2 EBV transforms T cells more successfully than B cells (Coleman et al. 2015). Host genes are differentially expressed following infection with type 1 compared to type 2 EBV strains, with *IL1β*, *ADAMDEC1* and *MARCKS* all significantly up-regulated following infection with type 1 compared to type 2 EBV (Lucchesi et al. 2008). There are other patterns of diversity across individual EBV genes, but they do not lead to such clear patterns of genome differentiation as the type 1/type 2 distinction (Palser et al. 2015).

To date, there are no whole-genome sequences of EBV isolated from patients with CAEBV. The number of EBV genome sequences from healthy individuals is also very small, which adds to the challenge of distinguishing disease-associated viral variants from normal variation. Studies of EBV variation in HLH (Kelesidis et al. 2012) have focused on small regions of candidate genes (eg LMP1 showing within and between group diversity in EBV sequenced from different populations (Tzellos and Farrell 2012)), but have been unable to distinguish variation that may contribute to disease from normal variation. Studies which aim to identify disease-associated viral variants would benefit from a case-control approach similar to that used in genome-wide association studies, comparing the EBV genome sequences of CAEBV patients with age and location-matched controls.

Primary Immune Deficiencies associated with severe EBV disease

Herpesvirus infections are particularly problematic for patients with monogenic defects of the immune system, and severe or persistent EBV infection is a hallmark combined or innate primary immunodeficiency. Among these diverse disorders there is a subset of conditions which appear to have a particular susceptibility to developing pathogenic consequences of EBV infection, and these are summarised below. Interestingly these disorders share a number of functional immune defects including cytotoxicity, T-cell receptor signalling, effective antibody production, cell migration and regulation of apoptosis (table 3). Investigation of patients presenting with severe or atypical EBV infection should focus on early identification of a possible PID or characterisation of an HLH or CAEBV clinical state. A proposed investigation algorithm is shown in figure figure 3.

Additionally several patients with combined immunodeficiency have chronic asymptomatic EBV viraemia. Optimal management of these patients is unknown, however careful long term monitoring is essential.

X-linked Lymphoproliferative Disease (XLP) / SAP deficiency

XLP-1 is a rare primary immunodeficiency first described over forty years ago (Purtilo et al. 1975) and the clinical features, which include HLH, lymphoma and dysgammaglobulinaemia, remain constant in more recently described cohorts (Seemayer et al. 1995; Sumegi et al. 2000; Booth et al. 2011). Overall mortality has reduced over time but HLH still remains fatal in the majority of patients with this manifestation (Booth et al. 2011). XLP results from mutations in the *SH2D1A* gene which encodes the SLAM-associated protein (SAP). SAP is an intracellular adaptor molecule expressed in T, NK and NKT cells and is a key regulator of normal immune function. Immune defects described in XLP patients include reduced or absent NKT cells (Nunez-Cruz et al. 2008), abnormal NK and CD8+ T-cell cytotoxicity (Parolini et al. 2000; Tangye et al. 2000; Dupre et al. 2005) and compromised reactivation induced cell death, all of which could explain the abnormal response to viral infection (Snow et al. 2009). Defective CD4+ T follicular helper cell function leads to impaired antibody function, and lack of memory B cells and long lived plasma cells (Veillette et al. 2008; Crotty et al. 2003; Qi et al. 2008).

Although XLP is associated with an increased susceptibility to severe EBV disease, the finding that up to 35% of patients are EBV negative at diagnosis supports our understanding of XLP as a disorder of severe immune dysregulation, with HLH, lymphoma and humoral abnormalities described in EBV negative patients (Booth et al. 2011). No significant difference in mortality was seen between EBV positive and EBV negative patients.

Management relies on appropriate treatment of HLH and lymphoproliferation, with most patients requiring immunoglobulin replacement therapy. Rituximab is routinely used to reduce EBV viral load. Survival following HSCT is 81% but mortality increases to 50% in patients with HLH. Survival for un-transplanted patients is reported as 63% but again outcome is extremely poor in the context of HLH with survival plummeting to 19% (Booth et al. 2011). A murine model of XLP has been corrected using HSC gene therapy and this approach may offer, in the future, an alternative treatment strategy for patients lacking a suitable donor for HSCT (Rivat et al. 2013).

XIAP deficiency

X-linked inhibitor of apoptosis (XIAP) deficiency is caused by mutations in the *BIRC4* gene and although initially described as XLP-2 due to similarities in clinical presentation to boys with SAP deficiency (Rigaud et al. 2006), it is now recognised as a more complex disorder of immune dysregulation with a wide spectrum of clinical manifestations. XIAP is ubiquitously expressed and appears to have several roles in immune cells including in NOD-1 and NOD-2 signalling pathways, involved in detection of bacterial infection, alongside its anti-apoptotic role (Aguilar and Latour 2015). Patients with XIAP deficiency have reduced NKT-cell numbers and lymphocytes demonstrate increased activation induced cell death (AICD). NK-cell cytotoxicity is normal (Marsh, Madden, et al. 2010). Diagnosis can be made through flow cytometric analysis of protein expression and genetic analysis. A functional assay demonstrating impaired TNFα production in response to NOD2 pathway stimulation in monocytes has also been described (Ammann et al. 2014).

A number of case series have now been published which confirm the main clinical features as HLH (which is often recurrent and of a more indolent course than seen in other FHLs or XLP), splenomegaly, colitis and periodic fevers (Pachlopnik Schmid et al. 2011; Yang et al. 2012; Speckmann et al. 2013; Aguilar and Latour 2015). In contrast to XLP patients, lymphoma has not been reported in patients with XIAP deficiency. Hypogammaglobulinaemia is also less common (67% vs 33%) (Pachlopnik Schmid et al. 2011) and has been described subsequent to EBV infection. Interestingly female carriers may also exhibit symptoms including erythema nodosum and inflammatory bowel disease (Dziadzio et al. 2015). The outcome for XIAP patients receiving HSCT following myeloablative conditioning is poor with historical data reporting a survival of 14% (Marsh et al. 2013). Mortality was due to transplant related toxicity in most cases highlighting the sensitivity of these patients to chemotherapy, likely related to the loss of XIAP's anti-apoptotic function. Results are more favourable with RIC; survival increases to 55% overall, and 86% if patients are in remission from HLH at the time of transplant (Marsh et al. 2013). Minimal intensity conditioning using anti-CD45 monoclonal antibodies has also been successfully employed (Worth et al. 2013).

ITK deficiency

Interleukin-2 inducible T cell kinase (ITK) is another recently described autosomal recessive PID associated with EBV-driven LPD, Hodgkin's lymphoma and, unusually, non-Hodgkin's lymphoma has also been reported (Huck et al. 2009; Serwas et al. 2014; Mansouri et al. 2012; Stepensky et al. 2011; Linka et al. 2012). ITK is a member of the TEC kinase family (which includes BTK) and is required for normal development and signalling in lymphoid cells. Progressive reduction in CD4+ T cells, naïve CD4+ T cells and NKT cell numbers is a common feature along with hypogammaglobulinaemia. Clinical features are primarily related to EBV associated lymphoproliferation but infections associated with T-cell deficiencies (*Pneumocystis jiroveci*, CMV, VZV and candida) have also been reported. 9 patients have been described to date, 8 presenting with LPD between the ages of 3 and 13 years (Ghosh et al. 2014). 6 patients have died with 5 succumbing within 2 years of presentation despite treatment, demonstrating the devastating course of this condition. Fever and lymphadenopathy were found in all patients with hepatosplenomegaly and significant lung involvement in 5/8 symptomatic individuals. The presence of autoimmunity in 3 and HLH in 2 suggests an underlying immune dysregulatory component to the disease but all patients so far have been EBV+ at diagnosis making it difficult to dissect out the role of EBV. Despite high viral loads the serological findings are variable, again suggesting an element of dysregulated immune response. ITK deficiency can be diagnosed through immunoblot to detect protein expression with confirmatory sequence analysis. The response to chemotherapy protocols to treat malignancy is variable. Some benefit has been shown for rituximab therapy and aciclovir but steroids do not appear to ameliorate the clinical features (Ghosh et al. 2014; Cipe et al. 2015). Two patients have received HSCT (1 MSD, 1 haploidentical donor) with one patient surviving (Ghosh et al. 2014). The optimal management strategy for patients with ITK deficiency is yet to be determined but close monitoring is essential.

CD27 deficiency

CD27 deficiency is a diagnosis to consider in patients with severe EBV disease, hypogammaglobulinaemia and recurrent infection. It is inherited in an autosomal recessive fashion. As an increasing number of cases are reported our understanding of the clinical spectrum of this disease is improving. CD27 is a member of the TNF receptor family and a co-stimulatory molecule important for the development T, B and NK-cells, in particular memory B cells. As CD27 is a widely used marker in the analysis of B and T cell subsets by flow cytometry, initial screening for this condition is both simple and reliable with all proven CD27 deficient patients having either absent

CD27 expression (9/11 tested) or severely reduced expression (2/11)(Alkhairy et al. 2015). Reduced numbers of NKT cells have been reported in severely affected individuals but impaired NK-cell function may be a more consistent immunological finding (Alkhairy et al. 2015). Impaired T-cell dependent B-cell responses due to defective CD4+ T cell help lead to compromised cellular and humoral immunity, and patients may be misdiagnosed with CVID (Salzer et al. 2013; van Montfrans et al. 2012). To date 17 patients have been described and it is apparent that the clinical phenotype is variable ranging from asymptomatic absence of memory B-cells and hypogammaglobulinaema, to EBV driven HLH and LPD, with no genotype-phenotype correlation (van Montfrans et al. 2012; Salzer et al. 2013; Alkhairy et al. 2015). Median age at presentation of symptomatic patients was 6 years in this cohort (range 1-22 years) with a reported mortality of 29% (Alkhairy et al. 2015). Many patients received immunoglobulin replacement therapy, rituximab and appropriate lymphoma treatment. Three patients underwent RIC mismatched unrelated cord blood transplant and are alive with the longest follow up of 4.5 years. Close monitoring of asymptomatic patients is crucial to allow early intervention in EBV driven disease.

XMEN (X-linked, magnesium defect, EBV, neoplasia)

XMEN is a recently described serious PID caused by mutations in the *MAGT1* gene, encoding the magnesium transporter 1 protein (Li et al. 2011; Li et al. 2014). It is characterised by chronic EBV infection with high viral loads and increased susceptibility to lymphoma and LPD. To date 8 patients have been described with an age at diagnosis of 3-58 years (Ravell, Chaigne-Delalande, and Lenardo 2014; Dhalla et al. 2015). They do not appear to develop HLH or other overt features of immune dysregulation unlike the other X-linked lymphoproliferative disorders. A decreased CD4:CD8 ratio is a consistent finding, with abnormal TCR signalling but significant humoral defects have not been described (Li et al. 2014). Due to abnormal magnesium flux in NK and T-cells, although viral specific cells are produced they fail to function sufficiently to control EBV infection. Patients have been reported to develop other viral infections such as Molluscum, HSV and VZV alongside recurrent sinopulmonary infections (Ravell, Chaigne-Delalande, and Lenardo 2014). Haematological malignancy is reported in all post-pubertal patients described, with many experiencing LPD earlier in life, and recurrent malignancy described in 2 patients.

Two patients received HSCT at the ages of 23 and 45 years but both died in the early post-transplant period from transplant related complications (Li et al. 2014). There is a suggestion from *in vitro* data and use in 2 patients that oral magnesium supplementation can increase NK-cell cytolytic activity and EBV control and, although highly experimental, it appears safe and well tolerated (Chaigne-Delalande et al. 2013).

STK4 Deficiency

Serine threonine kinase 4 (STK4) (also known as MST1) deficiency is an autosomal recessively inherited combined immunodeficiency characterised by progressive CD4 lymphopenia. STK4 is a ubiquitously expressed constituent of the HIPPO signalling pathway, which regulates cell proliferation, migration and apoptosis (Zhao, Tumaneng, and Guan 2011). Specifically, in human immune cells STK4 plays a critical role in preventing lymphocyte apoptosis (Abdollahpour et al. 2012; Nehme et al. 2012), thymic egression (Tang et al. 2015) and leucocyte migration (Dang et al. 2016).

13 patients with STK4 deficiency are reported in the published literature (Nehme et al. 2012; Halacli et al. 2015; Crequer et al. 2012; Abdollahpour et al. 2012; Dang et al. 2016). Combining these patients with our experience of 3 unpublished cases (16 in total), 13 patients have been exposed to EBV, and 11 have developed chronic viraemia. 5 patients have developed EBV driven lymphoproliferation or malignancy at a median follow up of 11 years of age. Additionally, these patients have recurrent invasive bacterial infections, severe cutaneous viral infections, mucocutaneous candidiasis and autoimmune cytopenias. Immunologically they demonstrate a progressive CD4+ lymphopenia with impaired thymic output, increased susceptibility to apoptosis and a panhypergammaglobulinaemia suggestive of immune dysregulation (Abdollahpour et al. 2012; Nehme et al. 2012). Vaccine and antibody responses are characteristically normal, including a normal serological response to EBV infection. In some kindred, intermittent neutropenia and congenital cardiac defects have been described. 7 patients have been treated by HSCT. 4 patients died of a combination of infectious, toxicity related and GVHD complications, the remaining 3 patients are alive and well, and apparently cured of their immunodeficiency (Nehme et al. 2012; Dang et al. 2016).

CTP synthetase 1 (CTPS1) Deficiency

CTPS1 deficiency has been recently described in 8 patients, as an autosomal recessive combined immunodeficiency, caused by a defect in lymphocyte proliferation following antigen receptor stimulation (Martin et al. 2014). CTP synthesis contributes to the free cellular CTP pool, essential for efficient cell division. CTPS1 activity is induced following TCR activation, and deficiency results in a T-cell proliferative defect despite normal TCR activation signalling. Clinically, these patients are susceptible to severe viral infections, and bacterial infection with capsulated bacteria, suggesting both a functional defect of T-cell cytotoxicity and T-independent B-cell immunity. The clinical penetrance of immunodeficiency appears high, with the majority of patients presenting within the first 2 years of life. All patients developed chronic EBV viraemia, with 4/8 patients developing severe IM and 3/8 developing CNS LPD. 6 patients received an HSCT and 4 remain alive and well, and free of symptoms.

Coronin 1A Deficiency

Coronin 1A deficiency was originally described as a thymic egress defect causing T- B+ NK+ severe combined immunodeficiency (SCID)(Shiow et al. 2008). Like other immunodeficiencies caused by actin cytoskeletal defects, Coronin 1A deficiency impacts on a wide range of lymphocyte processes, including development, survival, TCR signalling, immune synapse formation and migration (Foger et al. 2006; Punwani et al. 2015; Mace and Orange 2014; Mugnier et al. 2008). Impaired calcium flux and f-actin accumulation at the immune synapse result in increased T-cell apoptosis, compounding the CD4+ lymphopenia. A total of 9 patients have been described with Coronin 1Adeficiency (Shiow et al. 2008; Moshous et al. 2013; Mace and Orange 2014; Stray-Pedersen et al. 2014; Punwani et al. 2015; Yee et al. 2016), the majority with a typical SCID clinical presentation. Patients have an immunophenotype of absent or low naïve T-cells, severely impaired T proliferative responses, normal levels of total immunoglobulins, and impaired (but not absent) vaccine responses. Unlike other forms of SCID, Coronin 1A deficient patient have normal volume thymic tissue. 5/9 patients have developed EBV driven B cell lymphomas, and generally these have been at an earlier age than in other susceptible primary immunodeficiencies, with 4/5 patients developing EBV-driven LPD prior to 15 months of age. 2 patients died of their lymphomas prior to HSCT. No patients have developed HLH or severe IM. 3 patients to date have been treated with HSCT. 1 is alive and well, but 2 died following HSCT (GVHD, relapsed diffuse large B cell lymphoma).

Activated Phosphatidylinositide 3-Kinase delta syndrome (APDS)

Gain of function mutations in the phosphatidylinositide 3-kinase delta (PI3Kδ) subunit p110δ cause a combined immunodeficiency of variable clinical severity, characterised by recurrent sino-pulmonary infections, increased susceptibility to viral infections, lymphoproliferation, progressive lung damage (bronchiectasis) and an autosomal dominance inheritance pattern (Angulo et al. 2013; Lucas et al. 2014). PI3Kδ is a lipid kinase which mediates the phosphorylation of PIP_2 to generate PIP_3, an important second messenger in the downstream signalling of T and B-cell antigen receptors, costimulatory receptors, cytokine receptors and some Toll-like receptors (Okkenhaug 2013). Unregulated activity results in hyperactivation of the Akt-mTOR pathway, which in patient lymphocytes results in excessive terminal effector differentiation, increased activation induced cell death in T-cells, impaired cytokine production and impaired immunoglobulin class switching in B-cells (Angulo et al. 2013; Lucas et al. 2014). The immunophenotype of affected patients shows progressive lymphopenia, impaired T proliferative responses, impaired antibody responses to capsulated bacteria, increased circulating transitional B-cells and raised IgM levels. Although neither haemophagocytic syndrome nor severe IM have been described in APDS, a high incidence of chronic EBV viraemia has been described (Kannan et al. 2015; Lucas et al. 2014). Of 43 patients with APDS described in the literature, 9 (21%) have developed haematological malignancy or LPD, of which 3 were EBV positive, and two were undefined (Crank et al. 2014; Angulo et al. 2013; Kannan et al. 2015; Lucas et al. 2014; Kracker et al. 2014; Hartman et al. 2015). Diffuse large B-cell lymphoma was described in 3 patients and Hodgkin's Disease in a further 3 patients. There is one published patient who has been successfully treated by HSCT and we have transplanted a second patient without complication (unpublished). Inhibition of mTOR activity with Rapamycin has been used to successfully ameliorate the disease and has improved the immunophenotype in patients (Lucas et al. 2014). With the availability of selective PI3Kδ inhibitors, pharmacological blockade offers an attractive line of treatment for these patients.

Radiosensitive SCID

Defects of the non-homologous DNA end joining mechanism result in T- B- NK+ SCID, but clinical severity of defects in this pathway are heterogeneous, with several patients described with a hypomorphic phenotype. Case reports for hypomorphic DNA ligase IV and Artemis gene mutations demonstrate susceptibility for EBV driven-LPD or diffuse large B-cell lymphoma, however HLH has not been seen (Woodbine, Gennery, and Jeggo 2014; Moshous et al. 2003; Toita et al. 2007; Enders et al. 2006). Although numbers are small for each of these conditions, the incidence of EBV LPD seems to be between 20-50% of described patients.

Ataxia Telangectasia (AT)

AT is an autosomal recessively inherited syndrome characterised by progressive cerebellar ataxia, oculomotor dyspraxia, oculocutaneous telangiectasia, immunodeficiency and susceptibility to malignancy. It is caused by mutations in the phosphatidylinositol 3-kinase family protein, ATM, which plays an integral role in DNA repair and cell cycle checkpoint control. The immunodeficiency in AT is highly variable, but usually combined with low immunoglobulin levels, defective polysaccharide antibody responses and mild CD4+ lymphopenia (Chopra et al. 2014). A recently published French registry study demonstrated a 19.1% incidence of lymphoma in patients with AT by 20 years of age. Approximately 1/3rd of these lymphomas were Hodgkins Diseases (all tested were EBV related) and 2/3rds were NHL (50% EBV positive) (Suarez et al. 2015). HLH, SIM or chronic EBV viraemia has not been described in AT.

CD16 deficiency

Although only 3 patients have been described with homozygous mutation in the gene coding for CD16, two have developed EBV related severe complications (prolonged IM (de Vries et al. 1996), EBV-associated B-LPD (Grier et al. 2012)). Patients have normal numbers of NK-cells, but impaired

NK-cell cytotoxicity, and effected patients suffered from severe viral infections (particularly VZV and HPV in addition to EBV).

Other Primary Immunodeficiencies with EBV susceptibility

Although all diseases with impaired T cell function or number will struggle to respond appropriately to EBV infection, there are several other PIDs which, whilst not having the high penetrance of EBV-associated disease of the above conditions, still frequently develop significant EBV pathology. Patients with Wiskott Aldrich Syndrome are at high risk of developing malignancy, particularly EBV-driven B cell lymphoma. Historical data suggests that without HSCT, over 10% of patients will develop malignancy with a median age of onset of 9.5 years (Sullivan et al. 1994). There are also occasional cases of EBV-driven HLH in Wiskott Aldrich Syndrome (Pasic, Micic, and Kuzmanovic 2003; Bode et al. 2015). Other monogenic disorders of NK-cells are also susceptible to severe viral infections. Autosomal dominant mutations in the transcription factor GATA2 lead to the MonoMac syndrome (monocytopenia, B and NK-cell cytopenia, mycobacterial susceptibility, myelodysplasia). This progressive disorder can result in chronic EBV viraemia, and EBV associated malignancies (Spinner et al. 2014). MCM4 deficiency is an autosomal recessive isolated NK-cell deficiency, caused by a proliferation and survival defect of terminally differentiated NK-cells (Gineau et al. 2012). 1/14 patients described has developed EBV-associated B-cell LPD (Gineau et al. 2012; Hughes et al. 2012). Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of impaired lymphocyte apoptosis. There is a linear risk of developing lymphoma with age, and at 30 years 15% of patients have developed lymphoma with almost all being EBV positive (Price et al. 2014). Two patients have also developed HLH (Bode et al. 2015). WHIM (Warts, Hypogammaglobulinaemia, Immunodeficiency and Myelocathexis syndrome) is characterised by a susceptibility to severe papilloma virus and herpesvirus infections. Two cases of EBV-associated LPD (fatal in one case) have been described (Chae, Ertle, and Tharp 2001; Imashuku et al. 2002).

Conclusions and Future Directions

Significant advances in recent years have increased our understanding of the host-virus interaction in EBV infection and better characterised the pathophysiology of severe and aberrant EBV infection. Treatment of these rare disorders, however, remains inconsistent and optimal therapeutic approaches are largely unknown. Ongoing identification of new monogenic PIDs with specific EBV-susceptibility, and further characterisation of the phenotype and natural history of already described conditions, will aid management strategies for these patients. For patients without a discernible immunodeficiency, biomarkers to predict severe disease progression and those patients who would benefit from early HSCT are urgently needed. With improving understanding of the pathophysiology of these conditions, identification of targeted biologic, cellular or small molecule therapies offers the best hope of managing these patients effectively and safely in the future.

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Figure Legends

Figure 1: The Epstein-Barr virus life cycle

Following initial infection (typically through saliva) EBV establish a biphasic life cycle within the host, allowing non-productive genome maintenance in situations of immune surveillance, termed the latent cycle, and reactivating to the productive, infectious lytic cycle when in situations of primary infection or immune suppression. EBV induces different stages of latency (in B cells of different differentiation states, with progressively less viral protein and RNA production as B cells become more differentiated / less activated. Individuals with chronic active EBV or other EBV genetic susceptibilities may be unable to mount an effective CTL or antibody response to lytically replicating EBV-positive cells, leading to high virus loads and constitutive immune activation. Abbreviations: VCA – Viral caspid antigen, EA- Early antigens, EBER – EBV encoded small RNAs, EBNA – EBV nuclear antigen, LMP – Latent membrane protein, T_{fh} – T follicular helper cell.

Figure 2: Clinical manifestations of EBV infection

Although the vast majority of EBV infected individuals have an asymptomatic or self limiting primary infection (infectious mononucleosis), rare individuals develop more severe clinical syndrome as a consequence of an impaired ability to control lytic or latent EBV infection, or a the establishment of latent EBV infection in aberrant (non-B-cell) types. These complications can be immune dysregulatory, leading to lymphproliferation and a local or systemic hyperinflammatory state, or they can be malignant. Increasingly it appears that these pathologies are closely linked, with dysregulated inflammatory responses driving EBV-induced malignant proliferation. As a consequent there is considerable overlap between many of the malignant and inflammatory EBV clinical syndromes. The relationship between these main syndromes is shown in the figure. Arrows represent clinical overlap or progression between individual clinical syndromes.

Figure 3: Clinical investigation algorithm for chronic or pathological EBV infection

We advocate an aggressive approach to the investigation of chronic EBV viraemia and pathological consequences of EBV infection. Establishing the detailed immune state of the host, and the pathophysiology of infection, facilitates close monitoring of patients, assists targeting therapies, and helps identify which patients may benefit from early stem cell transplant. The above algorithm provides an exhaustive list of investigation for patients presenting with EBV – associated haemophagocytic syndromes, CAEBV, chronic EBV viraemia, SIM, and EBV-driven malignancy. It provides a framework for selecting investigations according to an individual patient's clinical presentation and disease progress. We do not propose that every patient should undergo every investigation listed above. Management and assessment of these patients benefits from a multidisciplinary approach involving haematologists, immunologists, rheumatologist, Infectious diseases specialists, and specialist immunodeficiency and molecular genetics laboratory services. *Abbreviations: TRECs – T-cell recombination excision circles, IgGAME – IgG, IgA, IgM, IgE, DHR - dihydrorhodamine assay, NBT - nitroblue tetrazolium assay, EM – electron microscope, FBC – full blood count, LDH – Lactose dehydrogenase, sCD25 – soluble CD25, PID – Primary Immunodeficiency*

, fHLH – familial HLH, WES – whole exone sequencing, WGS – whole genome sequencing, ANA – antinuclear antigen autoantibody, dsDNA – double stranded DNA autoantibody, ENA – Extractable nuclear antigen autoantibodies, Urinary alb:creat – urinary albumin : creatinine ratio, CMV – cytomegalovirus, HSV – Herpes simplex virus 1 and 2, VZV – varicella zoster virus, HHV6/7 – Human herpes virus 6 and 7, HIv – human immunodeficiency virus, BM – bone marrow, VCA – Viral caspid antigen, EA- Early antigens, EBER – EBV encoded small RNAs, EBNA – EBV nuclear antigen