DR SPUR'S MYSTERY CASE

HSV – can it be a clue to an underlying inborn error of immunity

Welcome to Dr Spur's Immunology Clinic
Referral letter:

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Dear Dr Spur

I was recently contacted by a wife, concerned about her previously healthy 54-year-old husband, who suddenly complained of a severe headache. She noticed that he had difficulty speaking and seemed to be off balance. I arranged with a specialist physician at the nearest hospital for emergency admission. A diagnosis of herpes simplex virus (HSV) type-1 encephalitis was made. The patient made a full recovery after a full course of intravenous acyclovir.

During the COVID-19 pandemic, it quickly became apparent that while most persons with SARS-CoV-2 infection had mild disease, some individuals were at risk of severe disease manifestations. The emerging literature supports a likely role for genetic factors in severe SARS-CoV-2 infection.

Considering the role of genetic factors in severe SARS-CoV-2, I now wonder if I should be looking for an inborn error of immunity in this patient. Can inborn errors of immunity be associated with severe viral infections such as HSV –1 encephalitis?

Kind regards
Dr Doolin

Dear Dr Doolin

Viral infections are exceptionally common and a frequent reason for healthcare consultations.[1,2] It is expected that preschool children will experience six to ten viral infections in the upper respiratory tract a year, while adults will experience an average of two to five common colds annually.[3,4] Susceptibility to viral infections and disease severity can certainly vary from one individual to the next, as you pointed out.[1]

The clinical outcome of a viral infection depends on the complex interaction between the virus and the host's immune responses.[5] In some instances viruses can employ immune evasion strategies to avoid detection by defence mechanisms, typically resulting in persistent or latent chronic viral infections.[5] Genetic variation or inborn errors of immunity (IEIs) that alter host factors can affect one or more pathways that are required by the host defence to gain control over a particular viral infection. This accounts for the variability in the clinical presentation.[1,5] As a result, viral infections in persons with IEIs may either be more severe than otherwise anticipated or give rise to the persistence or recurrence of viruses that would otherwise cause self-limiting illness.[6]

Advances in the field of molecular genetics and a deeper understanding of viral pathogenesis have enabled us to characterise those IEIs associated with increased host susceptibility to viral infections.[6] The host defence mechanisms against viral infections include:

- physical barriers (such as the skin and mucous membranes);
- antiviral restriction factors;
- innate immune responses (eg interferon and natural killer cells), and
- adaptive immune responses (including cell-mediated T-cell responses and humoral neutralising antibody responses).[5]

IEIs that alter any of these components may either predispose a person to multiple viral and other microbial pathogens or enhance only their susceptibility to one or more particular viruses, as outlined in Table I.[5]

Defective innate immune responses are responsible for many specific predispositions to viral infections, as outlined in Table I – typically with disruptions in viral pattern recognition pathways and natural killer (NK) cell defects. Interestingly, components of the innate immune response are frequently targeted by viral immune evasion strategies: for example, interferon regulatory factor 3 (IRF3) inactivation by the human immunodeficiency virus (HIV) and herpesviruses. IRF3 facilitates pattern-recognition receptor (PRR) signalling, which triggers type-I interferon (IFN) release, a critical component of the inflammasome and one of the first responders to invading pathogens.[10,11] Cytotoxic NK cells play a particularly important role in antiviral host defence by recognising and destroying infected cells and releasing cytokines such as Interferon-gamma that facilitates interaction with other components of the immune system such as adaptive immunity.[12] Whereas humoral immune deficiencies may also predispose to viral infections, cellular T-cell responses play a particularly important role due to the intracellular nature of viral infections.[2,5]

Given the common occurrence of viral infections, it can prove difficult to decide whether investigation for underlying IEIs is indicated. As I always say, it should raise suspicion when an infection is more **S**evere than otherwise expected, or is **P**ersistent, has **U**nusual features or is **R**ecurrent (**SPUR**). This is especially the case if the patient is treated and then **R**eturns **I**n **B**ad **S**hape (**RIBS**)!

As an example, the clinical features of infectious mononucleosis associated with primary Epstein-Barr (EB) virus infection may initially be difficult to distinguish from familial haemophagocytic lymphohistiocytosis (HLH) due to overlapping findings.[13] Fever, splenomegaly, hepatitis and thrombocytopaenia can be expected in uncomplicated infectious mononucleosis. However, should these signs be more severe than expected (eg complicated by coagulopathy or liver failure) or persist for longer than expected (eg fever and cytopaenia) or be accompanied by unusual findings such as central nervous system (CNS) manifestations, the diagnosis of HLH due to possible underlying genetic susceptibility should be considered.[2,13]

Age and the spectrum of susceptibility should also be considered. Patients with underlying severe combined immunodeficiency (SCID) affecting multiple components of the immune system typically present with life-threatening infections early in life owing to a wide spectrum of pathogens. In contrast, patients with a genetic susceptibility to a narrower spectrum of viral infections may be older and otherwise healthy.[1,5]

Genetic susceptibility to respiratory viral infections

It is known that underlying comorbidities such as chronic cardiac and pulmonary diseases can increase the risk of severe infection with respiratory viruses such as influenza A, respiratory syncytial virus (RSV) and severe acute respiratory syndrome-2 (SARS-CoV-2) virus. But complications have also been noted in otherwise healthy individuals.

It has been demonstrated that IEIs, particularly those affecting the IFN pathway, may increase the risk of severe infections with these pathogens. Interferon regulatory factors (IRFs) play a key role in the regulation of type I IFNs (IFN-I) and IFN-inducible genes. Mutations leading to a loss of IRF7 and IRF3

TABLE I: INBORN ERRORS OF IMMUNITY PREDISPOSING TO VIRAL INFECTIONS[1,2,5–9]

	Affected gene/mutation or type of IEI	Spectrum of viral susceptibility & associated clinical presentation
Risk of severe infections to multiple pathogens, including viruses	**Inborn errors affecting innate and adaptive immune responses**	
	SCID	Multiple viruses (also bacteria and fungi), eg respiratory viruses, chronic EBV, CMV, enteroviruses Risk of infection with live vaccine viral strains, eg poliovirus
	Atypical SCID or CID	
Increased susceptibility to specific virus(es)	**Inborn errors affecting innate immune responses**	
	TLR3	HSV-1 encephalitis
	TLR3, IRF7	Severe Covid 19 Severe influenza
	MDA5	RSV pneumonia Rhinovirus
	Autophagy genes ATG4A & MAP1LC3B2	Recurrent HSV-2 (Mollaret's) meningitis
	RNA polymerase III (POL III) defect STAT3 deficiency (hyper IgE syndrome) or IFNGR1 mutations	VZV encephalitis, vasculitis and pneumonitis Severe zoster
	TCM6, TCM8, and CIB	β-papilloma viruses • Epidermolysis verruciformis
	Inborn errors affecting adaptive immune responses	
	• Familial HLH with EBV susceptibility • XLP syndrome o XLP1: Mutation in SLAM-associated protein (SH2D1A) o XLP2 (BIRC4) • Other: LYST, RAB27A, AP3B1, ITK, MAGT1, CD27 • Familial HLH disorders triggered by EBV • PRF1, UNC13D, STX11, STXBP2	EBV • Fulminant infectious mononucleosis • HLH • Lymphoproliferative disorders • Chronic active EBV
	TNFRSF4	Human herpes virus 8 (Kaposi's sarcoma)
	X-linked agammaglobulinaemia (XLA) – BTK gene mutations	Severe/chronic enterovirus infections
	Inborn errors affecting innate and adaptive immune responses	
	GATA2 (myeloid transcription factor)/MonoMAC	Severe *Herpesviridae* infections (including HSV, VZV and CMV) Human papilloma viruses (warts) Severe molluscum contagiusum
	T cells and/or NK cells dysfunction due to defects in DOCK2, DOCK8, MHC II, CARMIL2, ORA1/STIM1, STK4, CXCR4 (WHIM), CARD11, CTPS1, MCM4, GINS1, RTL1, FCRF3A, MAGT1, CD27, CD70, STAT5B, and POLD1	Severe *Herpesviridae* infections Human papilloma viruses (warts) (DOCK8 & CXCR4/WHIM) Severe molluscum contagiusum (DOCK8, STK4)
	NOS2 defect	Predisposition to disseminated CMV disease

SCID: severe combined immunodeficiency; CID: combined immunodeficiency; CMV: cytomegalovirus; EBV: Epstein-Barr virus; TLR3: toll-like receptor 3; HSV: herpes simplex virus; IRF7: interferon regulatory factor 7; COVID-19: coronavirus disease; MDA5: melanoma differentiation-associated gene 5; RSV: respiratory syncytial virus; ATG4A: autophagy-related protein 4A; MAP1LC3B2: microtubule associated protein 1 light chain 3 beta 2 ; RNA: ribonucleic acid; STAT3: signal transducer and activator of transcription 3; VZV: varicella zoster virus; IFNGR1: interferon gamma receptor gene 1; HLH: hemophagocytic lymphohistiocytosis; XLP: X-linked lymphoproliferative; SLAM: signalling lymphocyte activation molecule; TNFRSF4: tumour necrosis factor receptor superfamily member 4; MonoMAC: monocytopenia and mycobacterial infection; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis; NOS2: nitric oxide synthase 2.

function have been shown to predispose individuals to severe influenza A infections. Toll-like receptor 3 (TLR3) gene defects can also interfere with IFN-I responses and have been linked to increased susceptibility to influenza viruses. IRF-7 and TLR3 defects have subsequently also been associated with susceptibility to severe SARS-CoV-2 infections.

Defects in pathogen-recognition components that affect the IFN pathway downstream may also increase susceptibility to respiratory viruses – for example, the cytosolic sensor melanoma differentiation-associated protein 5 (MDA5) mutations, which have been associated with recurrent or more severe RSV and rhinovirus infections.[1,5,14]

Genetic susceptibility to viral skin infections

The incidence of warts due to human papillomaviruses reaches

levels as high as 12% in the general population. But when warts (whether common, plantar or genital) are recurrent, severe or resistant to treatment, the possibility of genetic susceptibility should be considered.[2] Particularly severe forms of papillomavirus infections, including *epidermodysplasia verruciformis* and the so-called 'tree-man' phenotype with giant verrucae, are associated with CD28 deficiency (a T-cell costimulatory molecule).

Epidermodysplasia verruciformis is associated with susceptibility to beta-papillomaviruses, which do not usually cause clinically apparent lesions in the general population.[1,6]

Other IEIs associated with increased susceptibility to human papillomaviruses include DOCK8 deficiency and the WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) which results from a CXCR4 mutation, in addition to others listed in Table I.[2] DOCK8 deficiency is also associated with atopy, other cutaneous viral infections (eg herpetic lesions and molluscum contagiosum) and laboratory findings such as low IgM, elevated IgE and IgA, eosinophilia, poor memory B-cell responses and impaired specific antibody responses.[2] The fact that T-lymphocytes play a vital role in the host defence against viral skin infections is clearly demonstrated by the effect that defective T-cell responses have on host susceptibility.[9]

Genetic susceptibility to *Herpesviridae*

The family of *Herpesviridae* is renowned for establishing true viral latency and reactivation.[15] Latency is established in sensory neurons in the case of

- human alphaherpesviruses (herpes simplex viruses (HSV) 1 and 2 and varicella zoster virus (VZV));
- mononuclear cells in the case of human betaherpesviruses (cytomegalovirus (CMV);
- human herpesvirus-6 (HHV-6 and HHV-7), or
- B-cells in the case of human gammaherpesviruses (EBV and Kaposi's sarcoma–associated herpesvirus (KSHV).

The *Herpesviridae* maintain latency through a complex process of downregulating viral proteins otherwise expressed during lytic infection and by expressing microRNAs that influence host gene expression to avoid recognition of the latently infected host cell.[15] Reactivation can occur during either a period of stress (eg fever, trauma or UV radiation) or immune suppression (impaired T-lymphocyte function in particular), which enables the virus to replicate actively and possibly spread to new hosts.[15]

IEIs, whether they affect either innate or adaptive pathways, may predispose an individual to either more severe or atypical primary infections with viruses of the Herpesviridae family, severe or unusual reactivations or frequent recurrence of disease manifestations. Severe manifestations of primary VZV infection, including encephalitis, pneumonitis and vasculitis, have been associated with RNA polymerase III (POL III) mutations. In such manifestations, AT-rich DNA in the VZV genome cannot be sensed by host immune responses, which leads to inadequate IFN-I and IFN-III responses.[1]

In contrast, defective adaptive immune responses may predispose individuals to severe primary EBV infection. EBV infections in early childhood are frequently asymptomatic, whereas the clinical infectious mononucleosis syndrome is more likely to occur if primary EBV infection occurs during adolescence or in young adults.[16]

X-linked lymphoproliferative disease 1 (XLP1) predisposes otherwise healthy individuals to EBV-related lymphoproliferative disorders, which can include fulminant infectious mononucleosis, chronic active EBV infection, HLH, EBV-positive diffuse large B-cell lymphoma and EBV-positive T-cell lymphoma.[16,17] Other IEIs linked to severe EBV manifestations (eg meningitis and pneumonia) and lymphoproliferative diseases include defective signalling molecules ITK and also MAGT1, DOCK8, CARMIL2, IRF8, IL21R and PI3KR1 deficiencies.[16,17]

Whereas the risk of Kaposi's sarcoma is well described in the case of advanced secondary immunodeficiency associated with HIV infection, it may also occur in IEIs due to IFNGR1 and WASP mutations, with primary reduction in CD4+ T-lymphocyte counts.[17]

HSV-1 is well known to be the most common cause of sporadic viral encephalitis globally; it may occur either during primary infection or as a result of viral reactivation.[1,18] The outcome of HSV-1 encephalitis can be devastating, with a mortality rate of up to 70% if left untreated and a high rate of long-term sequelae.[19]

Severe life-threatening infections: high level of clinical suspicion required

As shown in this case, it is important to maintain a high level of clinical suspicion if a patient presents with a decreased level of consciousness, fever, headaches, seizures, focal neurological deficits and features such as new-onset aphasia or behavioural changes.[18,19] The pathogenesis is most likely associated with direct tissue damage as a result of lytic HSV-1 infection and inflammatory responses.[18] HSV-1 is ubiquitously present in the population and causes mostly asymptomatic to mild infections.

A severe life-threatening infection in an otherwise healthy person, especially in the context of viral reactivation, suggests an IEI as the likely cause. The defect most probably involves the TLR3 pathway, as shown by the emerging literature on HSV-1 encephalitis affecting paediatric populations.[1,18] TLR3 is a PRR that detects ds-RNA produced during viral replication and it activates the IFN pathway.[1] Furthermore, an X-linked recessive NFκB essential modulator (NEMO) deficiency and a STAT-1 deficiency both affect IFN production; both have been linked to HSV-1 encephalitis.[1,17,18] Notably, these IEIs differ from those associated with a genetic susceptibility to cutaneous HSV-1 manifestations (including DOCK8, STK4 and GATA2) owing to the different components of the immune system that play a predominant role in immune defence in different organs in the body.[17] It is generally accepted that TLR3 exerts control over cellular intrinsic immunity in the forebrain.[17]

Virus–host interactions: a deepening understanding

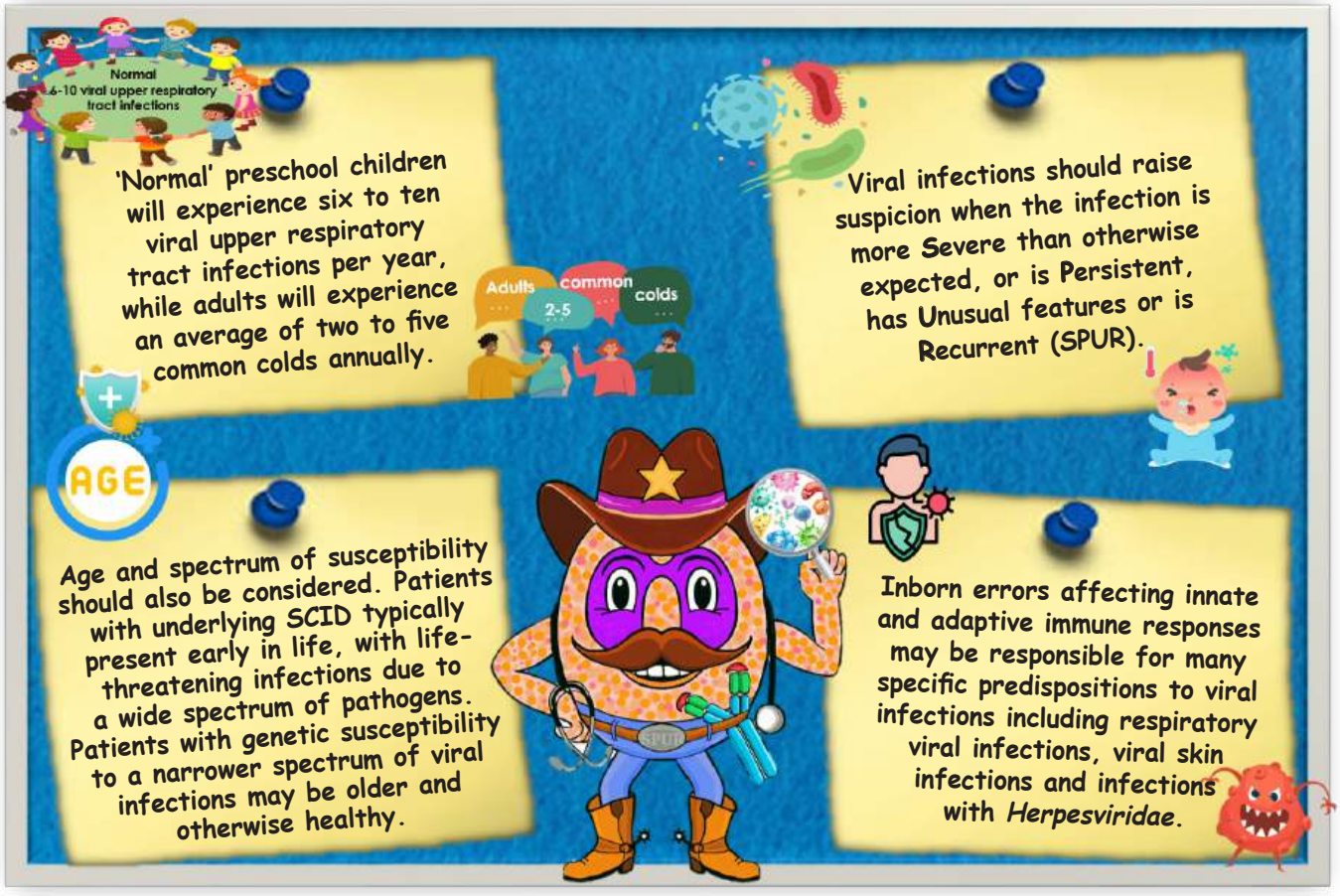
As we move deeper into the era of genomic medicine, our understanding of the complexity of virus–host interactions is deepening. When patients present with severe, persistent, unusual or recurrent viral infections, we should certainly entertain the possibility of an underlying IEI. In patients with severe viral infections, the following should suffice in the phenotypic laboratory workup: baseline immunoglobulins, specific antibodies with vaccine responses, lymphocyte subsets with naïve and memory T-cells, and lymphocyte proliferation studies (LPT) to mitogens (in babies) and LPT to recall antigens Candida, tetanus and varicella (in patients >1 year) with MBL levels.

Moreover, genetic testing for IEI is becoming more accessible and should be considered in cases such as this patient, who presented with a severe viral infection. This should be considered not only to characterise the risk and possible genetic susceptibility to other pathogens, but also to contribute to our understanding of the association of a particular disease with specific genetic polymorphisms.

Yours truly

Dr Spur

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

HSV and other viral infections can be a clue to an underlying inborn error of immunity

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