

Is Cytomegalovirus a Neglected Pathogen in the Field of Immunobiology?

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Abstract

Around the world deaths are behaving in a unique way which was previously thought to be impossible, namely, they are showing on/off switching. In switch-on they suddenly jump to a new higher level, stay high for around 12-months, and then switch-off back to the baseline trajectory. This behaviour originates at small (neighbourhood) area level and aggregates to give regional and national events whose magnitude depends on the degree of small-area synchrony. This mini-review explores the possibility that the common immune-modifying virus cytomegalovirus may be involved in these events

Keywords: Deaths; Medical admissions; Sickness absence; Infectious spread; On/off switching; Cytomegalovirus

Introduction

Evidence has recently emerged that deaths in all Western countries are behaving in a way previously thought to be impossible, in that they are showing on/off switching [1]. At switch-on deaths suddenly jump to a higher level, they stay high for around 12 months, at which point switch-off occurs and deaths revert to the lower baseline position. Deaths then stay at baseline until the next switch-on event.

Clearly something must trigger switch-on. Interestingly, medical admissions to hospital [2], hospital staff sickness absence [3] and in-hospital deaths all show the same behaviour [4]. This behaviour arises exclusively at small-area (neighbourhood) level indicating the possible transmission of a pathogen along social networks. Males and females behave as separate compartments and certain social groups appear more at risk of infection [5,6]. Persons with Alzheimer's and dementia show the highest mortality during these events [7], followed by those with lung infections [8].

The Link between Deaths and Medical Admissions

The link between deaths and medical admissions occurs via the nearness to death effect, where around half of a person's lifetime hospital admissions and bed occupancy is compressed into the last year of life, irrespective of the age at death [9]. The intrinsic high volatility in deaths therefore drives the marginal changes in admissions and bed occupancy, which explains why forecasting hospital demand has been such a problematic issue. The last year of life witnesses a rapid decline in cognitive and functional ability and increasing dependence on carers for assistance [10,11].

Hence any agent capable of tipping a susceptible fraction of the population into their last year of life would create the curious 12-month duration for switch-on observed in deaths and medical admissions, although deaths somewhat understandably lag admissions, i.e. acute illness precedes ultimate decease. This explains the relationship with staff sickness absence via exposure to patients.

Which Pathogen(s) could be Involved?

Hence, we have a seemingly transmissible agent capable of triggering illness in otherwise healthy hospital staff and of increasing medical admissions and deaths, mainly in the elderly.

Indeed, the agent must have a subtle effect in order to avoid detection. Bacteria would almost certainly be detected, leaving a virus as the most likely cause. Influenza has been rejected as a possible cause since persistent infection would be required to create a 12-month duration switch-on effect.

Clearly, any persistent virus could qualify, and most of the herpes viruses are widely prevalent around the world and have periods of reactivation.

However, based upon the range of medical conditions (including certain cancers) associated with each event, cytomegalovirus (CMV) has been suggested as a possible candidate. The following are relevant [12-17].

1. Despite assurances in medical textbooks, CMV is increasingly being diagnosed as a cause for a wide variety of acute illnesses in the seemingly immunocompetent patient
2. High levels of CMV IgG with inflammation are associated with substantially higher population mortality – a necessary condition for the observed higher deaths
3. CMV has a largest genome of all common viruses which is dedicated to diverse aspects of immune manipulation
4. CMV is now recognized as both oncomodulatory and oncogenic
5. CMV exerts aspects of immune modulation whilst seemingly 'dormant'
6. Infection and reinfection with multiple CMV strains are common
7. CMV is known to cause localized mini-outbreaks
8. Infants and children shed CMV for many months and can therefore act as super-spreaders
9. CMV is central in the expression of the infectious burden, i.e. the action of multiple acquired pathogens

10. English GP's have a 0% success rate at diagnosing patients with a CMV infection

While the above list does not conclusively prove that CMV is the causative agent, it suggests that it is likely to be a strong contender. A recent study using CMV infection in rhesus macaques has demonstrated that subclinical infection simultaneously alters host immunity, the gut microbiota and vaccine responses [18]. Such studies suggest that CMV is certainly capable of the diverse changes required to lead to switch-on in a susceptible fraction of the population.

Preliminary calculations indicate that around 20% of the population may be sensitive to the effects of the agent [8] and this suggests that genetic factors may also be involved. Indeed, certain strains of CMV are more prevalent in some countries than others [12-17].

Clearly no pathogen acts in isolation, and with over 1,400 known human pathogens [19], it would be surprising if the actual agent was not acting in concert with other persistent pathogens (the infectious burden), and CMV is a common denominator in many studies investigating the role of the infectious burden upon specific diseases [12-17].

If CMV is the causative agent, dedicated immune and genetic studies will need to be involved to elucidate how subclinical infection can alter the course of a variety of diseases. Even if CMV is not involved we need explanations as to how population health can show on/off switching, and such investigations will almost certainly involve new understanding relating to wider immune system balance and switching between alternative steady states [20].

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