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Narcolepsy risk and COVID-19

Response to Fernandez FX, Flygare J, Grandner MA. Narcolepsy and COVID-19: sleeping on an opportunity? *J Clin Sleep Med*. 2020;16(XX):XXX–XXX. doi:10.5664/jcsm.8520

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We appreciated the comment of Fernandez et al. [1] on the need to conduct more research on narcolepsy as a side effect of pandemic H1N1 vaccination ten years ago. Although much progress has been made suggesting a primary T cell mechanism is involved in narcolepsy[2-5], why one type of vaccine, Pandemrix, an AS03 adjuvanted vaccine used in Europe, was particularly involved and not others, is still not clear[6]. It has been hypothesized but not proven that this was because vaccination with Pandemrix occurred in Scandinavian countries at the specific time when wild type infections were also occurring, as explained recently in a thorough report of the International Alliance for Biological Standardization [7]

As new COVID-19 vaccines will also be rapidly deployed in, the risk that something similar might occur has been raised. This concern became more acute with the revelation that the Glaxo Smith Kline (GSK) AS03 adjuvant or other strong adjuvants may be used in the development of COVID-19 vaccines and that these vaccines are likely to be used in areas where COVID is still occurring. The hypothesis that AS03 alone was responsible for the narcolepsy side effect of Pandemrix is unlikely as a vaccine with AS03 but a different viral protein extract, Arepanrix, did not increase narcolepsy risk in Canada where it was deployed. The fact flu infections independent of vaccination was also a likely trigger in some countries also makes the AS03- only hypothesis unlikely [7,8]. AS03 is especially potent at stimulating $CD4^+$ T cell responses and data to date suggests that narcolepsy is the result of an initial $CD4^+$ T cell response that targets H1N1 flu sequences that subsequently get confused with hypocretin fragments. It is thus more likely that a combination of flu sequences and AS03 was needed for narcolepsy to manifest. Specific differences in viral protein extracts may also have been important [9 6].

Importantly, as population density increases, and we are encroaching more and more on natural habitats, new threats are likely to emerge so that rapid vaccine intervention may be increasingly needed. Thus understanding the scientific basis for the association of narcolepsy and potentially other immune mediated events with vaccines will be increasingly important. We would like to offer the following comments.

Vaccines are one of the safest and most effective ways to prevent disease. With access expanding in developing countries, they are also likely to be more and more widely used. Unlike antibiotics or antiviral drugs, vaccines do not induce resistance and can be adjusted to target new strains. The COVID-19 crisis has boosted investment in novel vaccine development especially in DNA, RNA- or viral vector-based vaccines [10]. While these vaccine platforms offer the potential of rapid development, and such deployment will always be key for rapidly emerging epidemics, it also carries risks.

The immune system is a very complex organ, not unlike the brain. It is strongly modulated by both nature and nurture, thanks to adaptive immunity. The general concept of seeing the immune system as all good or bad is outdated. Aspects of the immune system activation or inhibition can clearly be good and bad depending of the context. An insufficient response to infection can certainly be bad (frequent with aging), but an excessive response can also be bad, as seen in autoimmune diseases, antibody mediated enhancement in Dengue hemorrhagic fever [11], or in the much publicized "cytokine storm" acute respiratory distress syndrome (ARDS). Clearly, we need to stimulate certain components of the immune system while sparing others specifically in each specific case.

Similarly, for many years the brain has been considered an immune privileged organ like the eye and semen, mostly because autoimmune disorders affecting the brain were uncommon. This is also clearly not true. Autoimmune ataxia or encephalitis are recognized more and more frequently (many were first described in the context of paraneoplastic syndromes) [12 13]. Further, viruses and bacteria can penetrate the brain, and may target specific neurons, as exemplified by polio. Finally, we are now also discovering that neurodegenerative diseases such as Parkinson's disease have strong immune gene associations [14]. Neuroimmunology is becoming an exciting new area, also because some of these diseases such as Morvan's fibrillary chorea or anti Iglon-5 have major sleep symptomatology [15] and may offer new entry points into our understanding of sleep disorders. As this field advances, it will also allow us to better understand the immune etiology of diseases such as narcolepsy.

For vaccines, the goal is most often to induce a B cell/antibody response as once established it will be the first line of protection. It may thus be important to calibrate the immune response so it is not too strong or too weak. Problematically however it is impossible to do this without an associated T cell

response, and even more so in the presence of novel sequences in the case of a new organism, as recruitment of $CD4^+$ naïve T cells is needed (the development of an antibody response involves a $CD4^+$ T cell response first). In this context, adjuvants are likely useful in some cases because for unknown reasons some viral strains are inducing stronger responses than other. Further, adjuvants are not all the same [16], and may stimulate more strongly sub pathways of the immune system of interest to the immune responses of some but not all pathogens. Thus in the future, we are likely to require complex adjuvanted vaccines to counter disease [16].

In this complex context, it is an illusion to believe that vaccine can ever be 100% effective and 100% safe. In pharmacology, one learns "no effect, no side effect"-anything biological active can produce problems and it is always a cost benefit analysis. Every year in the US, patients develop kidney disease, deafness or allergic reactions to antibiotics and nobody expect 100% safety. The difference in vaccine vs drugs is that in the former scenario, we are not treating a disease, but rather vaccinating large numbers of healthy people so it is ethically different. The truth is that vaccines are incredibly safe, but as anything biologically active, they carry small risks. In case of a pandemic we may need to tolerate higher risk because the urgency is greater and the disease morbidity and mortality, as with COVID-19, is usually high. Nobody was to blame for the Pandemrix-narcolepsy situation. It was just unpredictable, bad luck, but it is important to understand something similar could occur again. Further, the response to the Pandemrix-narcolepsy crisis, could have been better.

What did we learn about narcolepsy and Pandemrix that could be useful?

First, what happens during infections should guide what to expect seeing with vaccine. In the case of narcolepsy, it is increasingly clear that H1N1 and other upper airway infections can also trigger narcolepsy. Had we known this, we could have looked for narcolepsy more carefully as a possible side effect and risk could have been identified earlier. For COVID, lists of Adverse Events of Special Interest (AESI) have been prepared based upon the known disease manifestations and these should be looked for carefully as vaccines are introduced. One of these is the multi-organ vasculitis in children that may be autoimmune and looks like Kawasaki's disease [17], a syndrome that had been linked to coronavirus infections in the past. The mechanism here could very well be the same as narcolepsy: an excessive T cell response in children who have an immature immune system. Importantly, although we can do our best to try and anticipate what adverse events might follow COVID-19 vaccine (if any), it will be important to have multi-national collaborative programs in place to identify unanticipated adverse events following vaccination and to quickly evaluate them.

Second, populations like the young before during puberty, young adults and the old are very different immunologically so a trial in one context cannot generalize; the three groups may need to be studied in small trials to compare the immune response before generalizing. Further, safety studies in small numbers are not predictive for rare events that can only be detected in large phase IV studies conducted after a vaccine is introduced. We must thus monitor carefully all though deployment and better pharmacovigilance should be part of the development of any vaccine. If the goal being heard immunity, it would be important to carefully plan with epidemiologists and statisticians how to deploy vaccination in what group and at what speed. We would also argue that we must keep blood samples from patients (pre/post) and vaccine batch samples all through the process to be able to learn from any mistake. After the Pandemrix-narcolepsy crisis, precious samples were destroyed, and it has been incredibly difficult to obtain vaccine samples for research.

Third, more basic research aiming at understanding vaccine effects and side effects is needed. Academic research is needed to ensure objectivity and independence. Immunology is one of the disciplines that has been progressing the fastest, because the tissue of interest, blood, is easily accessible. For example, it may be surprising but no large scale GWAS has ever been done on vaccination responses for vaccines we use routinely, although coordinating effort in this direction are ongoing; our narcolepsy studies strongly suggest immune genes will be strong modulators. We also need to study specific infectious diseases and vaccines before another pandemic arise. MERS and SARS were warning shots for COVID-19 and we did not listen. Zika has been a warning shot, many arbovirus can have very

devastating effects and again we did not listen. There is Ebola and, as mentioned above, antibiotic resistance to worry about. Vaccine are here to stay, we need to be better at explaining, preventing and understanding these diseases.

Fourth, once narcolepsy was identified as a side effect of vaccination, physicians were unable to provide state of the art symptomatic therapy. Many patients were young and such a clinical picture had rarely been seen except in few specialized centers in the world. Bureaucratic issues made it difficult for patients to get the best treatment. This may have been the biggest failure of all, as treating rapidly these children has a huge effect on long term prognosis, preventing the development of morbid obesity and developmental delays. These delays often have had irreversible effects on the life of these children and their family for no good reason.

Finally, COVID-19 offers interesting opportunities for the study of sleep and circadian tendencies in relative isolation and a more flexible schedule. The immune system is also strongly regulated by circadian timing and sleep insufficiency and experiments are likely to flourish in the near future. As the crisis continue to evolve, be a good citizen and keep your other vaccinations up to date.

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