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Review Article

Measles and Antibody-Dependent Enhancement (ADE): History and Mechanisms

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Abstract

Antibody-dependent enhancement (ADE) is an inadequate response to reinfection or vaccination. ADE was described for influenza and dengue fever: patients already exposed are likely to develop a more severe infection when exposed to a virus of another type than the first. Vaccine antibodies also appear to be responsible for an increased risk of severe disease in a naive person. In COVID-19, ADE is likely with antibodies acquired following infection or vaccination. The aggravation of the disease by measles vaccination has been shown for the inactivated virus vaccines. Atypical measles was also described after the live attenuated vaccine (LAV). ADE mechanisms are the penetration into cells of virus-antibody complexes promoted by FcγR or complement receptors and by an imbalance between neutralizing and facilitating antibodies. The role of maternal antibodies in ADE has been suggested after influenza vaccination in piglets. Facilitation of virus entry into the cell by complement fixation and an imbalance between anti-hemagglutinin and anti-fusion protein antibody levels have been suggested as a mechanism for atypical measles after the inactivated vaccine. Antibodies induced by the current LAV can induce ADE in vitro by binding to FcγR and the same imbalance. A recent vaccination campaign during an outbreak and the comparative history of measles before and during the vaccine era may alert to a possible ADE by the current LAV: it could be caused in infants by maternal antibodies and in adults by waning vaccine immunity. Improvement of current LAV or the development of a new type of vaccine could eliminate this phenomenon.

Introduction

The phenomenon of antibody-dependent enhancement (ADE) is an "inadequate" response to an infection due to a previous infection (or vaccination) with a related virus (or perhaps a bacterium in the case of pertussis). This response is considered inadequate by theoretical immunology in which antibodies have a protective role against infection. However, when infected with rubella, measles, varicella, common cold, mumps, and polioviruses, agammaglobulinemia patients develop a normal disease and are perfectly resistant to reinfections as are immunologically competent persons.[1] This shows that antibodies are not essential to fight these infections and acquire lifelong protection against them. Theoretically, the role of antibodies in general and more specifically in viral infections should be rethought.[2]

In this manuscript, we will review the viruses that cause an aggravated (or atypical) infection phenomenon following an ADE due to antibodies acquired after an infection or a vaccination.

Concerning measles, ADE has been suggested to explain cases of atypical measles occurring after an inactivated vaccine. Rare cases of atypical measles have been reported after the live-attenuated vaccine (LAV). A massive vaccination campaign amid an epidemic was followed by an outbreak of deaths among infants and young children in Samoa in 2019.

Proposed mechanisms for atypical measles after the inactivated vaccine and after LAV are reviewed to explain the rare cases of atypical measles after the live vaccine. The role of maternal antibodies may explain the deaths in Samoa. Vaccine strategies that could avoid this phenomenon will be briefly discussed.

Historical background

The phenomenon of "antigenic original sin" was first described at

Keywords: Measles; Antibody-dependent enhancement; Inactivated vaccine; Attenuated vaccine.

Abbreviations: ADE, antibody-dependent enhancement; LAV, live attenuated vaccine.

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the end of the 1940s: more influenza was observed when infected with a wild virus heterologous to a previous vaccination. This was the first mention of the paradox of an inadequate immune response in persons previously infected with a related virus.[3,4]

Dengue

This is a disease transmitted by the *Aedes aegypti* mosquito (the mosquito that transmits yellow fever, dengue, chikungunya, and Zika). It is caused by the dengue virus, a Flavivirus. The first observation of more severe dengue in some patients was in 1964 in Bangkok, Thailand.[5] This has been observed: at the beginning, the disease was benign and classic, then a worsening was noted after a few days. This severe dengue was called dengue with hemorrhagic fever (DHF). This form of dengue fever was observed in children under 1 year of age and in patients with a secondary antibody response (patients with pre-infection anti-dengue antibodies indicating a previous infection). To observe this phenomenon, an interval of 3 months to 5 years between successive infections was required. In children under 1 year of age, cases were observed more between 6 and 9 months of age, when maternal antibodies were considered insufficient to protect the child.

The authors already noted that it was unlikely that the immunodependent facilitation of acute viral diseases was the sole property of a single group of viruses. They referred to similar observations following measles or respiratory syncytial virus vaccinations with an inactivated vaccine followed by wild virus infections. We will see that they were right. The same phenomenon was described in Cuba in 1981.[6] In 1977, a dengue epidemic affected 500,000 people and in 1978, 44% of Cubans had anti-dengue antibodies. In 1981, an epidemic of dengue of another serotype (caused by a related virus that has moved away from an antigenic point of view) occurred and caused 116,143 hospitalizations. The same clinical and immunological characteristics as in Thailand were observed (with the denomination DHF/DSS: dengue hemorrhagic fever followed by dengue with shock syndrome).

The same Cuban team[7] explains in 2010 these observations by the phenomenon of ADE, *i.e.* "antibody-dependent enhancement".

The immunity against the disease is specific to the viral type (there are 4 for dengue) and lasts for life. There is cross-immunity with other subtypes which decreases rapidly with time. In infants, maternal antibodies decrease rapidly and go through 3 phases: neutralization of the virus, facilitation of the viral infection, and degradation of antibodies. The longer the interval between successive infections in adults and children, the more severe the disease is, because the antibody level is lower. Infants get severe dengue when the antibody level drops below 1/20. There is a facilitation of the entry of the virus into the cell by residual antibodies but also modification of the expression of inflammatory cytokines and intracellular antiviral mechanisms, innate and adaptive immunity are altered.

Probable mechanisms of ADE

Xu *et al*.[8] provide a summary of the mechanisms of ADE in certain viral infections. The first explanation proposed was that of complexes formed by the virus and antibodies, capable of binding to the FcR receptor on the surface of cells: this binding would have led to increased virus entry. The cells involved capable of producing ADE in this case are monocytes, macrophages, dendritic cells, and some granulocytes. This ADE is mainly mediated by IgG, but IgM, IgE, and IgA are also able to induce it. ADE can also be due to complement activation by the virus-antibody complex: entry into the cell is then via the complement receptor. Many cell types express complement receptors on their surface (complement is a set of serum proteins involved in immune reactions). This complement fixation by ADE will allow the virus to attack cells that are not its usual target and thus lead to an atypical and more severe disease: fibroblasts and endothelial cells are able, like immune cells, to fix the main complement protein, C1Q.[9] It has been shown that this pathway facilitates certain viral infections (Ebola virus, certain Parvoviruses).[10] Finally, there is iADE (intrinsic-ADE) which modifies the cellular antiviral response following the binding of Fc to FcR: the expression of IFN-β and IL-10 is modified. Taylor *et al*.[11] stated that to achieve neutralization of a viral particle requires an antibody concentration above a certain threshold: below this threshold, there may be a facilitation of infection (ADE).

The ADE is found in many viruses like Alphavirus, Flavivirus (Chikungunya, Ross River Virus, Sindbisvirus, Dengue, and West Nile Virus), and respiratory viruses such as Coronavirus. ADE occurs only in some infected patients and only for a short window of time depending on the antibody level. About the influenza virus, the phenomenon of ADE has been shown for successive infections, or vaccination prior to an infection, or via maternal antibodies, and this in animals: rodents, ferrets, and pigs. In the case of Respiratory Syncytial Virus (RSV, Paramyxovirus, same family as measles), more severe disease is observed in vaccinated children when compared to those who had the disease before. For the Ebola vaccine containing a protein of the viral envelope, the ADE was described by complement fixation: a large number of cell types become target cells of the virus.

Wen *et al*. describe the 5 classical presumed ADE mechanisms for coronaviruses (unlike dengue virus, ADE in SARS and MERS are not triggered by a heterovirus strain, but the certainty is the effect of both have negative influences on the human body and are probably an obstacle to the development of viral vaccines): concerning the 3 mechanisms described above, he distinguishes 2 different mechanisms involving complement (C1-q or C3 dependent) and mentions the enhancement of the fusion of viruses and cells via a change in the conformation of viral protein through its binding with antibody.[12]

Data from the study of SARS-CoV and other respiratory viruses suggest that anti-SARS-CoV-2 antibodies could exacerbate COVID-19 through ADE.[13] This ADE was shown by animal trials of SARS-CoV-1 vaccines from 2003.[14–16] Recently, studies on the COVID-19 virus have shown a non-canonical ADE mechanism independent of Fc receptors. Antibodies directed against a specific site on the NTD (N-Terminal Domain) of the SARS-CoV-2 spike protein were found to directly increase the binding of ACE2 (Angiotensin Converting Enzyme2, cellular virus receptor) to the spike, thereby increasing the infectivity of SARS-CoV-2.[17–19]

Problem with the Dengvaxia dengue vaccine

The higher occurrence of severe dengue in vaccinated (compared to unvaccinated) had been noted in the Sanofi clinical study as early as 2015.[20] Publications in 2016 warned against the massive vaccination campaign undertaken in the Philippines in 2016–2017.[21,22] Despite this, a massive vaccination campaign started in 2016 in the Philippines and resulted in the death of more than 100 children from severe dengue.[23] From now on, the WHO recommends vaccinating only people who have already been infected by dengue and not people who are naive to this infection.

In 2017, two articles were published in Science that again expose this phenomenon. They describe the increased risk of severe

dengue in vaccinated young children compared to those who received a placebo. In addition, the large number of cases of severe dengue (DHF/DSS) in children 6–12 months of age, when maternal antibodies drop below a certain threshold, is consistent with the ADE hypothesis. Katzelnick demonstrates that a specific range of DENV (dengue virus) antibody titers in the circulation correlates with the risk of severe dengue in subsequent infection.[24] Feinberg[25] describes ADE as a mechanism based on increased binding and internalization of antibody-coated infectious virions by Fc receptors (FcRs, antibody-binding sites expressed by specific immune cells, including DENV target cells).

Measles

Measles is an infection that confers lifelong protection,[26,27] and there is only one virus serotype (it is accepted that all sera from infected or vaccinated individuals react with all measles viruses, so this ADE phenomenon is only likely to occur as a result of a vaccine that would not confer this strong and long-lasting immunity).

Atypical presentation and worsening of the disease by measles vaccination was shown and accepted for the first inactivated virus vaccines in 1965 and later.[28–31] Atypical measles[32] presents as an unusual rash, high fever, and pneumonia, and was first described in 1965 and reported as a natural infection after the use of an inactivated vaccine. The typical rash begins at the hairline and spreads to the face and trunk, followed by Koplick's spots. The atypical rash begins at the extremities, without Koplick's spots. Typical measles appeared between 5 and 9 years of age, atypical between 10 and 14 years.

Atypical measles was also described in the 1970s after LAV,[32–35] but it was not always more severe than the classical disease.[36,37] A case of atypical measles has even been described in a 29-year-old man without previous measles immunization.[38] According to Sabella,[39] modified measles can occur in those vaccinated with LAV or in infants who have residual maternal antibody levels. In Ukraine (2016) and Samoa (2019), the sharp increase in cases just after the start of a massive vaccination campaign amid an epidemic has not been explained and could be considered in the light of one of the mechanisms proposed above (the role of maternal antibodies below a certain threshold).[40,41]

Probable mechanisms of atypical measles

As early as 1967 Fulginiti *et al*.[30] proposed that atypical measles could be due to antibody levels that have become too low over time: delayed hypersensitivity induced by an inactivated vaccine can result in atypical measles when antibody levels have fallen too low and are no longer protective. The accelerated humoral response to the virus in a person who has received the inactivated vaccine would lead to the formation of immunocomplexes (virus-antibodies) depositing in the lungs with subsequent tissue damage.[42] According to Frey and Krugman,[43] inactivated vaccine-related atypical measles is characterized by the high level of anti-HI (anti-hemagglutinin) antibodies maintained during convalescence, in contrast to typical measles. According to Polack *et al*.[44] in monkeys, the inactivated vaccine (and not the live vaccine) causes atypical measles in a re-challenge. Unlike the antibodies induced by the LAV, those induced by the inactivated vaccine are transient, of low affinity, and their avidity does not mature with time. After a challenge with the measles virus, persons vaccinated with the inactivated vaccine have high levels of complement-fixing antibodies: antibody-complement immune complexes are deposited and cause atypical measles, the low-affinity antibodies produced are unable to neutralize the virus in cell culture. The same author[45] stated in 2007 that the most widely accepted hypothesis is that atypical measles after inactivated vaccine results from an imbalance in the antibody response to the virus glycoproteins (hemagglutinin HA and fusion protein F or hemolysin). The method of virus inactivation would remove epitopes: antibodies produced against the hemagglutinin of the inactivated virus would have a low neutralizing capacity. The inability of inactivated measles vaccines to prevent infection may be due to the absence of an envelope component responsible for the production of anti-hemolysin antibodies (or fusion protein).

This ADE mechanism was confirmed in 2006, this time with the LAV. In a publication from the Mayo Clinic,[46] the authors show *in vitro*, on human and murine cells, that antibodies induced by live attenuated measles vaccine are able to induce ADE by FcγR binding. Measles vaccine virus can override pre-existing immunity through facilitating antibodies: this phenomenon is dose-dependent and occurs for low antibody levels or low-affinity antibodies (such as those elicited by vaccination due to the decrease over time in antibody levels). The authors note the importance of the balance between anti-H (hemagglutinin) antibodies that promote ADE and anti-F (fusion protein) antibodies that prevent ADE. The interest of this publication is not to question the vaccine but to demonstrate that the immunity conferred by the vaccine does not hinder its use as an anticancer agent (the measles virus would have a selective activity on tumors, without damage to healthy tissues)[47] (in passing, we will notice in this publication that the live attenuated virus of the vaccine can form syncytium of fused cells despite the presence in the patients of anti-measles antibodies induced by a previous vaccine).

In summary, the inactivated measles vaccine has caused atypical measles, probably related to ADE, with proposed mechanisms involving the level and balance of certain types of antibodies induced by the vaccine. Rare cases of atypical measles (not always aggravated) have been reported following the current LAV, the same mechanism has been proposed recently. Wouldn't this atypical measles after LAV be more frequent? They could go unnoticed because they are not always more severe than typical measles. Couldn't the rare cases of severe measles observed in the vaccine era be due to ADE?

To try to answer this question, we must compare the severity of measles before and after mass vaccination. In the pre-vaccine era, virtually all children developed measles by age 12; young women passed on their strong immunity to their newborns.[48] In the vaccine era, measles is an "adult vaccine disease" according to Gregory Poland,[49] and it can be quite severe according to 2019 CDC statistics: it requires hospitalization in 10% of cases and causes complications in 5% of cases. In the USA, from January 1 through December 31, 2019, 1,282 individual cases of measles were confirmed in 31 states. Of these cases, 128 were hospitalized and 61 reported complications, including pneumonia and encephalitis. All measles cases were caused by wild-type D8 or B3 measles. It should be noted that the vaccine virus types A and no longer circulates naturally: the circulating wild viruses are of different types.[50]

Measles in the pre-vaccine era

What was the real severity of measles in the pre-vaccine era: 3 documents seem to indicate a benign disease in general and especially in the age group where it seems to become worrying nowadays, young adults. To document measles in young adults, one must look for outbreaks in islands that had not had measles for a long time and therefore where the adult population was not immune.

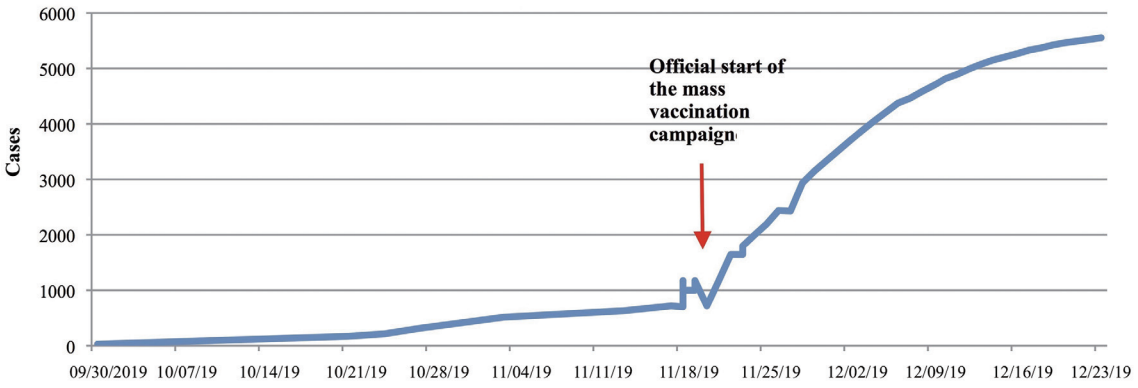

Fig. 1. Evolution of the outbreak as a function of time cumulative cases. Cases of measles during the Samoa outbreak (October-December 2019), were plotted day by day according to official reports and in the major Anglo-Saxon press.

Measles in the Faroe Islands in 1846: most of the deaths were under 1 year old, see page 21 of the report,[26] the peak of mortality was then between 50 and 60 years old. There was no increased mortality between the ages of 1 and 20, but it began to increase around the age of 30 (page 21). It has been hypothesized that lifelong immunity to measles depends on repeated stimulation of the immune system by encounters with a circulating virus: in the Faroe Islands, there was no epidemic between 1781 and 1846; in 1846, people over 65 years of age did not become ill. So repeated stimuli are not necessary for robust immunity, a single encounter with the wild virus seems to be necessary. Measles epidemic in 1882 in Iceland:[51] During the 1882 epidemic, after 35 years without measles, no atypical measles was noted, no statistics are published but it is understood that the disease was mild in patients aged 4 to 20 years. Measles epidemic 1893 in Samoa:[52] Most deaths were due to gastrointestinal diseases, no deaths were observed when a proper diet was followed (deaths seem to be more due to poor eating habits). There had been 2 successive influenza epidemics which had weakened the population already very susceptible to respiratory infections.

Frequency of complications of measles in 1963:[53] This survey carried out in England and Wales on the measles epidemic between January 1 and April 30, 1963, aimed to identify the complications of the disease. Here is a summary: complications were found in 0.8% of the estimated measles cases during this epidemic. Of which 0.16% were pneumonia (7 children died, 3 of whom had severe comorbidities). Of which 0.04% were neurological complications with a total of 61 encephalitis cases (0.014% of total measles cases), the deaths observed were found in people with severe comorbidities. As a result of these complications, no chronic neurological disease was identified in healthy individuals prior to the epidemic. One child was found to be comatose and no significant sequelae were reported. The decedents were individuals with high pre-outbreak morbidity. As a reminder in 2019, measles in the US causes complications in 5% of cases.

It is difficult to compare the historical period with the current one because the former is less documented and medicine has made enormous progress since the pre-vaccine measles era; the comparison of these 2 eras does not exclude that in rare cases vaccination is capable of causing severe measles at ages where it did not in the pre-vaccine era.

Last measles outbreak in Samoa

Can the phenomenon of worsening infection by vaccination explain the disastrous 2019 outbreak in Samoa? The measles outbreak in October-November 2019 is described in an article on the Aimsib.[41] In summary, the outbreak was declared on October 16, 2019, after a suspected case was identified on October 9, the mass vaccination campaign began on November 20, 2019.

Figure 1 was plotted with the official cumulative case count figures: the coincidence between the start of this vaccination campaign and the inflection of the curve on November 20 can be noted on this curve. The small breaks in the curve at this time are due to the inconsistent figures found between 19 and 22 November in the official reports and the major Anglo-Saxon press. This is the only time when the figures are inconsistent during the whole epidemic. The outbreak slowly started just before the mass vaccination campaign and then exploded after the mass vaccination started (if we trust the official documents that note the delivery of vaccines by UNICEF from October 1st but claim that the mass vaccination only started on November 20th).

One hypothesis concerns the vaccination of babies at 6 months. Indeed, the vaccination campaign that began on November 20 reached the entire population from the age of 6 months. The minimum age of vaccination was lowered from November 8, 2019, to 6 months. In studies on children of 6 months, vaccines are usually injected in high doses (to compensate for the lower immune response of young infants?). But the WHO recommended in 1993 to stop routinely vaccinating children of 6 months (some studies have shown too much toxicity at this age).[48] A large proportion of cases and deaths in Samoa are recorded in children under 4 years of age, contrary to other islands in the region. According to Iankov *et al*.[46] ADE may be explained by low antibody levels. The severe measles observed in Samoa in infants and young children could be explained by maternal antibody levels becoming too low.

The role of maternal antibodies

The blood of newborns contains maternal antibodies transmitted either through the placenta during pregnancy or through breast milk.[54] These antibodies can cause a phenomenon of facilitation (they increase the induced pneumonia), as demonstrated in vaccinated piglets whose mothers have been vaccinated against influenza.[55] Concerning measles, it seems that at 6 months 99% of children have an antibody level below the protection threshold, evaluated at 300 IU/ml. These children therefore still have low levels of antibodies that could cause ADE.[56] The transfer of immunoglobulins from mother to fetus is well documented but could be

extraneous to the immunity transmitted; indeed, as Francis Macfarlane Burnet pointed out in 1968,[57] measles immunity is independent of antibodies but depends solely on cellular immunity.[2] This was also shown for the VSV.[58] Maternal transfer of cellular and humoral immunity not related to immunoglobulins has been shown.[59] It is therefore possible that low levels of maternal antibodies are partly responsible for this post-vaccination outbreak, by aggravating the infection by the live vaccine virus in babies in Samoa.

Future directions

Atypical measles could be explained by the phenomenon of facilitation of infection by vaccine antibodies whose level decreases with time and which would present a lesser affinity with wild circulating strains: the vaccine was conceived against a virus isolated in the 1960s. Wild viruses are still circulating, have not been eliminated by vaccination, and are antigenically distant from the vaccine virus dating from the 1960s:[60] the currently circulating strains, although belonging to the same serovar, have moved away from the vaccine strain. Circulating wild-type measles virus strains (genotypes B, C, and D) may be partially resistant to antibodies induced by LAV from genotype A.[61]

The levels and specificity of antibodies present in persons with severe or atypical measles vaccinated with the attenuated vaccine should be explored. If the mechanism proposed by Iankov *et al*.[46] can explain these cases, then consideration should be given to modifying the LAV: either by adapting it to currently circulating strains or by deleting epitopes that may induce facilitating antibodies. Differences in strains and mode of production of LAV[62] should be studied concerning induction of atypical measles as well as genetic differences that may affect the type and level of antibodies produced. Other types of vaccines may be considered: according to Polack *et al*.[63] a DNA vaccine encoding measles virus glycoproteins does not cause atypical measles in a challenge in monkeys. Recombinant protein subunit vaccines or vectorized vaccines would provide partial protection but could be improved.[62]

Conclusions

The inactivated measles vaccine has caused atypical measles, probably related to ADE, with proposed mechanisms involving the level and balance of certain types of antibodies induced by the vaccine. In rare cases of atypical measles (not always aggravated) reported following the current attenuated vaccine, the same mechanism has been proposed recently.

Measles seems to be more severe in the vaccine era and not only because of the displacement phenomenon (from infancy to adulthood), since in young adults without immunity the disease seemed less severe in the pre-vaccine era. This aggravation could be explained by the phenomenon of facilitation of infection by vaccine antibodies (ADE: antibody-dependent enhancement), whose level decreases with time and which would present a lesser affinity with wild circulating strains: the vaccine was conceived against a virus isolated in the 1960s. Wild viruses are still circulating and are antigenically distant from the vaccine virus dating from the 1960s: circulating wild-type measles virus strains may be partially resistant to antibodies induced by the live-attenuated vaccine.

During the massive vaccination campaign amid the 2019 measles outbreak in Samoa, the many infants and young child deaths could be due to ADE caused by insufficient levels of maternal antibodies facilitating infection with the live attenuated vaccine. So, facilitation could occur in infants because of the persistence of low-rate or low-affinity maternal antibodies and in young adults because of the decrease of titers and/or low affinity of vaccine antibodies.

The levels and specificity of antibodies present in persons with severe or atypical measles vaccinated with the attenuated vaccine should be explored and other types of vaccines may be considered.

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Conflict of interest

The author has no conflict of interests related to this publication.

Author contributions

Banoun H. is the sole author.

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