Environmental Toxicology and Pharmacology 55 (2017) 8–13

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

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Vaccination is fundamental but can it escape from a more insightful and critical information about its action?

1. Background

Quite recently, the US President Donald Trump posted a tweet on the possible relationship between vaccines and autism; the circumstance was then reported in the journal Nature Seven Days (Nature, n 542, Feb 16th, 2017 p 276). Such news not only turned on a heated debate involving the US President's policy but raised new criticisms about vaccine safety, putting once again in the spotlight this fundamental medical concern. A lot of people are disposed to trust a causative relationship between autism and vaccines, probably because this belief encourages parents of autistic children to search for truth and hope for a successful therapy (Foster, 2017).

However, regarding the presumptive relationship between vaccination and the associated pathogenetic risk of autism, little evidence seems to support this view in the very recent scientific literature, which actually reported a major relationship between Thimerosal (the preservative containing mercury) and neurological disorders (Geier et al., 2010; Geier et al., 2016; Bjørklund et al., 2017a,b; Geier et al., 2017). Safety of mass immunization with mandatory vaccines is still a hot topic in current medicine (Stratton et al., 2001; Sykes et al., 2014; Basch et al., 2017; Mus et al., 2017). However, a correct knowledge and awareness about the activity of vaccines are certainly due, as misinformation can usually be shared even among professionals anytime and in a quite flawed way (Chhawchharia and Puliyel, 2014). For example, in Italy many researchers, such as Bellavite and Ortolani, actively involved in alternative and complementary medicine, are arranging an outcry against mandatory vaccination, even without having a renowned expertise in the field, so generating somehow controversies and misleading prejudices (Bellavite, 2015; Bellavite et al., 2007; Signorelli et al., 2017; Marti et al., 2017). Mercury is undoubtedly a risk factor for the pathogenesis of many neurological disorders, such as autism spectrum disorder (ASD), as it causes DNA damage (Bakulski et al., 2015; Chaari et al., 2015; Mortazavi et al., 2016; Pletz et al., 2016). On the other hand, the associated risk between vaccination and autism might not be confined exclusively to the controversial debate about mercury toxicology in Thimerosal. Although some attempt has been made in order to elucidate the time-course of the association between neuropsychiatric disorders and the vaccination schedule, many further studies are needed to provide a thorough comprehension of this concern (Leslie et al., 2017). Furthermore, the major issue of the aforementioned debate might not be represented by the existence of toxicants in vaccines, i.e. some contaminant or preservative with noxious activity, yet rather on the same activity of vaccination in a particular individual's immune "landscape", i.e. that immunization may create damages if the subject's immune microenvironment is impaired by environmental and external factors, the importance of which is usually skirted in a vaccine campaign.

2. Driving towards an immuno-toxicological perspective?

In few words, a vaccine should be considered fundamentally the introduction of an attenuated or killed infectious organism or parts of it in a living organism, in order to elicit a Th1-mediated response in the immunized subject and henceforth to generate an immunological memory and protective antibodies. This probably too simplistic definition should give insights on the role of external damage-associated molecular patterns (DAMPS) or pathogen-associated molecular patterns (PAMPS), present in vaccines, in the neuropathogenesis and the onset of neurodevelopment disorders. The same inoculation protocols pertaining different vaccines should encourage this speculative suggestion, particularly because it would compel anyone to pay attention about possible immune-mediated interferences (Nascimento Silva et al., 2011). For example, the commonest PAMP for toll-like receptor 2 (TLR2), such as peptidoglycan, traverses the placenta and although fetal brain does not seem to show signs of neuroinflammation or neuronal apoptosis, PAMPs induce the neuronal transcription factor FoxG1 causing an abnormal neuron proliferation and leading to a 50% greater density of neurons in the cortical plate, a circumstance correlated with abnormal cognitive behaviours following birth (Humann et al., 2016; Layton et al., 2017). Metals, which can be found in the environment also as pollutants, can change vaccine performance (Osendarp et al., 2007; Yalçın et al., 2011). In this context, also astrocytes, which participate in the neurodevelopment of the central nervous system (CNS), may be involved in the pathogenesis of neurological disorders when they are impaired in their major function (Blanco-Suárez et al., 2017).

During the Th1-mediated response to vaccines, microglia can release pro-inflammatory cytokines, reactive oxygen species, and proteases, then contributing to the exacerbation of the subsequent neuronal damage, particularly if producing alamins, such as S100B, which is regulated by the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1). S100B induces the upregulation of IL-1β, TNFα, and iNOS gene expression in microglia and the release of matrix metalloproteinase 9 and nitric oxide (Xu et al., 2016). The aforementioned alarmin signaling through PARP-1 is also elicited during zinc toxicity (Kauppinen et al., 2008). Interestingly, impairments in zinc homeostasis associated with disorders in the glutamate transmission lead to ischemic or neurodegenerative disorders (Pochwat et al., 2015) and environmental pollutants, rapidly introduced into the body as heavy metals conjugated with organic carriers, can impair immunity following vaccination (Lin et al., 2017). This evidence would suggest that the imbalance in the neuro-developmental plasticity and in the astrocyte-neuron cross-talk, causing also dysfunction in the synapses formation, might derive from impairments in the homeostasis between metallic oligo-elements and immune function, particularly in the complex relationship between astrocytes, microglia, and neurons (Pal and Prasad, 2014; Tiffany-Castiglioni et al., 2011). The existence of metallic components in vaccines might

http://dx.doi.org/10.1016/j.etap.2017.07.016
Received 10 May 2017
Available online 29 July 2017

yet represent a major concern for the individual's health, as relatively low levels of these compounds may create an ignition of neuroinflammation and imbalance in the astrocyte regulation of essential trace elements (Bulcke and Dringen, 2016). Furthermore, this circumstance should be of major importance particularly when heavy metals and other chemical pollutants are severely affecting the cellular response to stress, causing astrocyte functional impairment. This may occur in individuals living in developing countries, where metallic contaminants are widespread in groundwater and soil (Bjørklund et al., 2017b). While past reports have shown that supplementation of minerals through diet might not necessarily improve the immune performance of vaccination, to date this evidence is still under discussion, despite some positive data (Provinciali et al., 1998; Türk et al., 1998; Ahmad et al., 2016; Ivory et al., 2017). The relationship between metallic ions and innate immunity is therefore particularly complex, as it does not merely depend on dietary habits. This relationship needs to be clarified in order to shed a light on the mechanism by which astrocytes communicate with neurons, as the role of metalloproteinases is of particular importance (Saftig and Bovolenta, 2015; Cirillo et al., 2016). This overview should suggest for the existence a wider landscape to be considered in the debate about vaccines, particularly when talking about the possibility that vaccination can cause neurodevelopmental disorders in infants or children, even through the toxic activity of metal-containing additives. First of all, vaccination should take into account the environmental scenario in which any vaccine campaign is held. Countries with a huge concern about heavy metal pollution in the environment, either due to geochemical or industrial sources, should adopt a mandatory classification about the risk for human health caused by vaccination, particularly for neurodevelopmental disorders, on the basis of population exposure to pollutants. The environmental burden of the toxicant ethyl-mercury, for example, is a main cause of concern, as it may cause direct insults, such as blood-brain barrier (BBB) damage (Takahashi et al., 2017) but also interfere with the oxygen sensitivity of astrocytes (Angelova et al., 2015). A great deal of countries worldwide are addressing the great concern of mercury (Hg) pollution in the environment, due to the widespread existence of Hg-methylating microorganisms in soils and groundwater (Podar et al., 2015). When oxidative stress increases in astrocytes, due to a pro-inflammatory immune response induced by the expression of IL-1β, ROS trigger the expression of the matrix metalloproteinase 9 (MMP9), which exacerbates the neuronal damage. This expression is mediated through a c-src-mediated transactivation of the PDGFR/PI3K/Akt signaling cascade, which links the mechanism to a p47(phox)/NADPH oxidase 2/ROS signaling, leading to the final activation of MAPKs and the downstream activity of the transcription factors NF-κB and AP-1, which in turn enhance MMP9 promotion of astrocytes migration and tissue remodelling (Yang et al., 2015). This evidence would suggest that neuronal injury, caused by pollutants-mediated oxidative stress, might be exacerbated following the use of immunization by vaccines (Ankeny and Popovich, 2007). Particularly for those vaccines having a neurotropic targeting, the concern should be seriously taken into account. In this case, it would appear that the provocative issue raised by the US President Donald Trump might not be entirely out of the discussion.

3. The measles issue in Italy

Very recently in Italy, a public outcry occurred because of the Government's decision to increase the number of mandatory vaccinations. This uproar focused the main popular attention on measles epidemiology and its related vaccination, highlighting a significant concern, yet highly controversial, dating back many years before and regarding autism (Bellavite, 2015; Flaherty, 2011; Curtale et al., 2010; Pezzotti et al., 2013; Atti et al., 2017). Actually, the exacerbation of the discussion in the press and in the politic forums arose from a great misinformation about vaccines, particularly after the publication of Wakefield's retracted article in The Lancet in 1998 (Wakefield et al., 1998). The role of vaccines in the public health affairs, their action, the reliability of the research grounded underneath, the ability of science to reach people's awareness in the most correct and widespread way, the perception of a lacking in the fair and honest scientific discussion among peers, in order to improve vaccination efficacy and safety, the economic burden of vaccination and so on, inflated the most recent debate of the official medicine in Italy. Past data on epidemiology of measles in Italy showed that the average standardized annual incidence of this infectious disease was 75.1% (years 1971–1980), 83.0% (years 1981–1990) and 66.6% (years 1991–1996) and that after the introduction of measles vaccination at the end of 1970′s, the epidemiology of measles showed a great heterogeneity in the regional incidence, with different loco-regional serum prevalence values (Gabutti et al., 2002). This heterogeneity described both as measles incidence and as vaccine coverage, has never been deeply addressed in further investigations. The research appears to suggest that, based on the serum survey data after 1990's, immune subjects percentage increased from 25.5% to 70.7% (children years 1–9), probably because of both natural immunity and vaccine immunization (Gabutti et al., 2002). The regional inhomogeneity and existence of poor adherence to MMR vaccination in different areas have been partially associated with people misinformation and vaccine refusal, probably causing local measles outbreaks and raising public health concerns (Restivo et al., 2015). Actually, the complexity of measles epidemiology in Italy would raise some further comment. Table 1 shows the epidemiology (reported cases) and the vaccine coverage (1 dose early pediatric age within 24 months) in two representative Italian regions (with radically different percentages in cases and coverage) in the latest three years.

A first observation allows us to reach the consideration that there is no apparent direct association between vaccine coverage and reduction of a measles outbreak. Data collected from the Italian National Institute of Health report that the richest and most informed regions in Northern Italy such as Piemonte showed a dramatic reduction in measles cases, from 654 to 50 (years 2013–2016) despite the sensitive though small reduction in vaccine coverage (from 92.10% to 88.70%, 2013–2015 yrs), while apparently, in poorest and less informed regions in Southern Italy, e.g. Calabria, a reduction in vaccine coverage appears to be associated with an increase in measles reported cases (see Table 1)- However, it seems that difficulties in fully eradicating measles and new emerging cases are a great concern particularly in adolescents and adults, rather than pre-scholarly children (Filia et al., 2011, 2013). Difficulty in totally preventing and removing measles outbreak occurring in adolescents and adults is yet a great concern not only in Italy but in many further European countries, suggesting for new vaccination protocols (Wang et al., 2014; Shakoor et al., 2017). In endemic and developing countries, vaccination campaigns resulted in a sharp reduction of measles outbreaks, from the end of nineties to 2008, then reaching a new dramatic increase despite the vaccine high coverage from 2009 to 2012, particularly in adolescents, a circumstance rather similar for mumps and rubella (Shibeshi et al., 2014). Therefore, the question is if the actual vaccination protocol can reach a total vaccine coverage and high IgG-immune protection against measles (but against mumps and rubella) in the age 18–29 years or if new emerging outbreaks in adolescents have to be considered as the consequence of an immune sensitivity due to vaccination refusal in infancy. In other words, we are wondering why new cases are not prevented by vaccine coverage higher than 90%, due to natural immunity and vaccination campaign and if individuals' immune surveillance may be compromised by further causes than the simplest vaccine refusal. Despite the expanded debate in the scientific field, actual data do not appear to permit a full elucidation of this issue.