Madridge Journal of Vaccines

Editorial Article

Open Access

Vaccines, Autism and Rerum®

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Article Info

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doi: 10.18689/mjv.2017-104

Received: May 20, 2017
Accepted: June 17, 2017
Published: June 24, 2017

Citation: Ruggiero M*. Vaccines, Autism and Rerum®. *Madridge J Vacc.* 2017; 1(1): 15-19.

Published by Madridge Publishers

Abstract

In this Editorial, I comment the most recent peer-reviewed studies published on the topic of vaccines and autism and on the role of neuroinflammation and immune system dysfunction in the etiology of autism. I describe a novel tridimensional multi-linked supramolecular structure composed by chrondroitin sulfate, vitamin D_3 and oleic acid that aims at modulating the immune system and fighting systemic and brain inflammation and how it relates to the complementary approach to autism.

Key words: vaccines; autism; immunotherapy; GcMAF; inflammation

Vaccines and autism

The question of whether a causal or coincidental association between vaccines and autism exists is heating up in the past couple of years with protagonists of political life called into the debate as this article published in the British Medical Journal, entitled "Andrew Wakefield calls Trump "on our side" over vaccines after meeting" seems to imply [1]. The Author of this article refers to Dr. Wakefield, a British former gastroenterologist and medical researcher who, in 1998, co-authored a study reporting 12 cases of children with autism who had been vaccinated with the Measles Mumps Rubella (MMR) vaccine [2] thus implying an association between vaccination and the onset and development of autism. The article was retracted by the publisher in 2010 with the following statement: "Following the judgment of the UK General Medical Council's Fitness to Practise Panel on Jan 28, 2010, it has become clear that several elements of the 1998 paper by Wakefield et al. are incorrect, contrary to the findings of an earlier investigation. In particular, the claims in the original paper that children were "consecutively referred" and that investigations were "approved" by the local ethics committee have been proven to be false. Therefore, we fully retract this paper from the published record" [3]. Literal reading of the retraction note seems to imply that the major reasons for the retraction are to be found in the fact that the children had not been referred consecutively, and that there was not a valid approval of the study by the local ethics committee.

In the years following the heated debate on the safety of vaccines and, more in particular, on the association between MMR vaccination and autism, hundreds of studies have been published claiming that there is no association between MMR vaccination and autism. Out of the very many studies supporting such claims, a paper published in 2014 by Authors affiliated with the Centers for Disease Control and Prevention of the USA and with prestigious medical research institutions such as the Harvard Medical School of Boston, Massachusetts or the Vaccine Study Center of Kaiser Permanente of Northern California, is of particular interest [4]. In this article, the Authors report the observation obtained by the Vaccine Safety Datalink that is a collaborative project established in 1990 between the Centers for Disease Control and Prevention and nine primary health care organizations. Given the wealth of information that it is able to gather and analyze, the Vaccine Safety Datalink is instrumental in informing policy

makers and the public about the safety of the vaccines utilized in the USA and its observation and ensuing recommendations are often acknowledged in other countries. Thus, the researchers contributing to the Vaccine Safety Datalink" have published important studies demonstrating that childhood vaccines are not associated with autism or other developmental disabilities" [4].

However, despite the unanimous, strong, legally-binding and compelling statements by practically all Health Authorities of the entire world declaring that vaccinations are not associated with autism, some recent peer-reviewed papers retrievable in the official scientific database of the US National Library of Medicine of the National Institutes of Health, seem to cast doubts on these certainties. For example, a study published in December 2016 by Authors working in research institutions in Maryland and Texas, uses official data from the Vaccine Adverse Event Reporting System (VAERS) database to conclude that "the risk of autism during from the late1990s to early 2000s in the US significantly decreased with reductions in Hg exposure from Thimerosal-containing childhood vaccines" [5], thus implying that there was an association between Thimerosal-containing vaccines and autism. On the same wavelength is a study published in March 2016 by Authors working at the Center for Biotechnology, the School of Humanities and Social Science and at the Center for Biotechnology of South Carolina who write: "A comprehensive literature search has implicated several environmental factors associated with the development of ASD (Autism Spectrum Disorders). These include pesticides, phthalates, polychlorinated biphenyls, solvents, air pollutants, fragrances, glyphosate and heavy metals, especially aluminum used in vaccines as adjuvant [6]. A commentary on this paper written by K. Fluegge of the Institute of Health and Environmental Research in the USA in December 2016, further elaborates on this point as follows: "Exposure to thimerosal-containing vaccines may disrupt the activity of several endogenous targets as has been shown, principally including μ-opioid receptor" and "Future attention may need to be focused on understanding on how early-life mercury exposures, such as in vaccines, may or may not reveal a gestational opiate dependence induced from other ASD-implicated environmental factors" [7]. The association between organic mercury and abnormalities in brain development is also described in a study published in March 2016 by Authors working at Experimental Toxicology Services in The Nederland and at the Department of Plant and Food Sciences, Faculty of Agriculture & Environment of The University of Sydney, Australia. In this study the Authors write: "In children, methyl mercury exposure during pregnancy (in utero) has been associated with delays in reaching developmental milestones (e.g., age at first walking) and decreases in intelligence, increasing in severity with increasing exposure. Ethyl mercury exposure from thimerosal in some vaccines has been associated, in some studies, with autism and other neurological disorders in children" [8].

Rather intriguing are the conclusions of a study published in January 2017 by Authors working at the Department of Public Health Sciences of the Pennsylvania State University College of Medicine and at the Yale Child Study Center of the Yale University School of Medicine in New Haven. In this study, the Authors, after the premise that "the association of the measles, mumps, and rubella vaccine with autism spectrum disorder has been convincingly disproven", somehow surprisingly conclude that: "This pilot epidemiologic analysis implies that the onset of some neuropsychiatric disorders may be temporally related to prior vaccinations in a subset of individuals" [9]. Such a temporal association between vaccinations and autism is also described in a paper published in 2015 by Authors of the Sound Choice Pharmaceutical Institute in Seattle, Washington. In this paper, the Authors "assess the public health consequences of fetal cell line manufactured vaccines that contain residual human fetal DNA fragments utilizing laboratory and ecological approaches including statistics, molecular biology and genomics". In order to evaluate such consequences, they adopt a reverse logic approach that consists in analyzing MMR coverage and autism in a period when the coverage fell below 90% in three prominent countries of the Western world [10]. According to the Authors, "the average MMR coverage for the three countries fell below 90% after Dr. Wakefield's infamous 1998 publication but started to recover slowly after 2001 until reaching over 90% coverage again by 2004. During the same time period, the average autism spectrum disorder prevalence in the United Kingdom, Norway and Sweden dropped substantially after birth year 1998 and gradually increased again after birth year 2000".

Given such a plethora of contradicting observation, it is not surprising that the majority of videos (65.5%) in the unregulated social network You Tube™ discourages the use of vaccines as reported in January 2017 by Authors working at the Department of Public Health in Wayne, New Jersey and at Columbia University, New York [11]. These observation are further confirmed by a study of the University of California published in November 2016, where the Authors developed an automated method to study social media sites dedicated to discussions of parenting, reaching the following conclusions: "In most vaccination stories from the sites we analyzed, it is taken for granted that vaccines and not vaccine preventable diseases (VPDs) pose a threat to children. Because vaccines are seen as a threat, parents focus on sharing successful strategies for avoiding them, with exemption being the foremost among these strategies" [12]. Such an attitude toward vaccinations does not seem to be limited to non-professionals as suggested by a survey that took place in 2013 at San Diego State University, where the attitude toward vaccination of 1419 diplomats of the American Board of Integrative and Holistic Medicine was evaluated. Such a survey concluded that: "Integrative medicine physicians were less likely to administer vaccinations than physicians in traditional allopathic medicine. Among the 44% who provide vaccinations, 35% used alternative schedules regularly" and "Integrative medicine physicians were also more likely to accept a connection between vaccinations and both autism and other

chronic diseases" [13]. Interestingly, these concerns are not confined to the USA as demonstrated by a study performed by Spanish researchers from Madrid who, from November 2014 to March 2016. performed a study on children under the age of 16 not properly vaccinated. In this study, they report that "A total of 20 families were counselled. The median age of the children was 2 years, and 80% of them received no vaccine. Absolute non-acceptance of vaccination was practiced by 45% of parents. The main reasons for not vaccinating were: 100% thimerosal-containing, 90% risk of autism, 85% aluminum-containing, 70% presence of other stabilizers and preservatives, and 65% risk of anaphylaxis" [14].

Autism and neuroinflammation

Although the task of determining whether vaccines are associated or not with autism is well beyond the scope of the present article, one conclusion seems to be shared by most researchers: aberrations of immune system function and neuroinflammation appear to be common characteristics of autism spectrum disorders [15]. Thus, in a paper by Siniscalco *et al.* from the Department of Experimental Medicine of the Second University of Naples, Italy, it is clearly stated that: "Immune system dysregulation is well-recognized in autism and thought to be part of the etiology of this disorder" [16]. According to these Authors, the endocannabinoid system and macrophages are key elements in this context as they observed dysregulated gene expression of the endocannabinoid system in blood monocyte-derived macrophages obtained from autistic patients. In this paper, the Authors studied the role of a modulator of the immune system, the vitamin D binding protein-derived Macrophage Activating Factor (GcMAF), known to be clinically effective in autism, concluding that their data "point to a potential nexus between endocannabinoids, vitamin D and its transporter proteins, and the immune dysregulations observed with autism".

Two years later, Theoharides *et al.* [17] published a study in Translational Psychiatry supporting the hypothesis that immune dysregulation and brain inflammation play a role in the pathogenesis of autism and, therefore, anti-inflammatory and immune modulating compounds may be considered among the therapeutic approaches to the disease. Among immune modulating compounds, also these Authors quote GcMAF. This molecule has been of our interest for quite some time and we have published several papers on the effects of GcMAF on human monocytes [18], microglial cells [19], and neurons [20] as well as on the interactions between plasma glycosaminoglycans and proteins such as Gcprotein [21, 22]; therefore, in 2016 I published a novel hypothesis that may shed light on the mechanism of action of GcMAF in autism as commented by Theoharides et al. [17] According to this article, "the biological and clinical effects thus far attributed to GcMAF are indeed to be ascribed to a glycosaminoglycan, chondroitin sulfate, that binds both the precursor and the active form of GcMAF" [23].

The role of chondroitin sulfate in being responsible for the biological and clinical effects attributed to GcMAF in modulating the immune system and counteracting systemic and brain inflammation, is supported by the Mayo Clinic of the USA, arguably one of the most prestigious medical research institutions in the world.Thus, the Mayo Clinic states that there is strong scientific evidence for the clinical use of chondroitin sulfate as a supplement in osteoarthritis, a chronic disease characterized by systemic inflammation and derangement of immune system function. In conditions as diverse as coronary artery disease, psoriasis, muscle soreness or interstitial cystitis, that is in chronic conditions characterized by immune dysregulation and inflammation, the Mayo Clinic reports that there are clinical studies supporting its use, although further studies need to be performed. After these proposed uses supported by clinical studies, the Mayo Clinic lists the uses for chondroitin sulfate that are based on medical tradition or scientific theories. Such a list is rather long and, in alphabetical order, encompasses most of human diseases and conditions such as:

"aging, allergies, Alzheimer's disease, amyotrophic lateral sclerosis, antioxidant, antiviral, blood clots, bone healing, breast cancer, burns, cervical disc disease, chest pain, chronic venous ulcers, clogged arteries, colorectal cancer, diabetes, gout, gum disease, headaches, heart attack prevention, heart disease prevention, HIV/AIDS, hyperglycemia, high cholesterol, inflammation, inflammatory bowel disease, joint problems, kidney stones, leukemia, lung cancer, malaria, mouth and throat infections, multiple sclerosis, nerve damage, nerve regeneration, neuroblastoma, osteoporosis, pain, Parkinson's disease, premature birth prevention, quality of life (osteoarthritis), rheumatoid arthritis, snoring, soft tissue injury, spinal cord injury, spine problems, surgery, systemic lupus erythematosus, temporomandibular joint disorder (TMJ), transplants, wound healing" [24].

Therefore, based on these evidences, I concluded the article published in 2016 with the words: "... this hypothesis lays the foundation for the development of non-proteinic macrophage activating factors that are not extracted from human blood, thus avoiding all the risks associated with human blood-derived products" [23].

The Rerum®

It is based on these premises that I developed the Rerum® a tridimensional multi-linked supramolecular structure composed by chrondroitin sulfate, vitamin D_3 and oleic acid that aims at modulating the immune system and fighting systemic and brain inflammation. Thus, the Rerum® is composed by molecules each one of which is endowed with these properties. In addition to the immune-modulating, anti-inflammatory properties of chondroitin sulfate quoted above, it is worth noticing that also vitamin D_3 and oleic acid show superimposable biological effects that may be exploited in the context of autism. As of today there are more than 100 peer-reviewed studies retrievable from PubMed when searching for "autism and vitamin d", and more than 400 studies dealing with "autism and fatty acids". Out of these many studies, it is worth mentioning a very recent (February 2017) paper suggesting that: "... practitioners might consider treating autism with 300 IU/kg/day, and seek to prevent

autism by supplementing pregnant and lactating women (5000 IU/day) and infants and young children (150 IU/kg/day) ..." [25]. Also deign of note is a study on oleic acid and brain function reporting that: "... oleic acid promotes axonal growth, neuronal clustering, and the expression of the axonal growth associated protein, GAP-43" [26].

Although the properties of chondroitin sulfate, vitamin D_3 and oleic acid that may be useful in autism and, more in general, in neurological conditions, have been known for years, the Rerum® is an entirely novel concept that is based on a tri dimensional multi-linked supramolecular structure that amplifies the biological and clinical effects of each one of the molecules composing the structure. Thus, since they are arranged into an unitary structure, the three molecules are able to interact with their respective receptors on target cells at the same time and in the same constant molecular arrangement; in other words, one molecule of chondroitin sulfate, that is constituted by 50 - 100 repetitive units of N-acetylgalactosamine (the active site of GcMAF) and glucuronic acid, is linked via hydrophobic and hydrophilic interactions with a fixed number of vitamin D_3 and oleic acid molecules in a flexible superstructure and the three molecules interact with their respective receptor all at once. The single superstructure offers the advantage of amplifying the biological and clinical effects of the Rerum® enabling a three-prong attack on each target cell, an occurrence that could not occur if the three molecules constituting the Rerum® were administered independently of each other.

An important feature of the Rerum® is that it is composed by food supplements that have been used for decades and are generally recognized as safe; because of this feature, it is registered as a supplement in the European Union and Switzerland and it is currently used in the complementary approach to autism as well as to a number of other conditions ranging from cancer to pain, from autoimmune diseases to persistent Lyme that are conditions characterized by alterations of immune system function and inflammation. The biological and clinical effects observed with the Rerum® have been reported at the Fourth International Congress on Integrative Medicine that was held in Fulda, Germany, on April 1 and 2, 2017. As far as the results pertaining to autism are concerned, of particular interest were the data *in vitro* presented by Drs. D. Siniscalco and A.L.Brigida who described results consistent with those they had previously observed with GcMAF [16], thus confirming the hypothesis that chondroitin sulfate is the moiety responsible for the effects previously attributed to GcMAF. These results observed *in vitro* were matched by the clinical observation of Dr. Antonucci, a medical psychiatrist and researcher working at the Biomedical Centre for Autism Research and Treatment in Italy with a remarkable track record of publications in the field of immunotherapies of autism [27]. Dr. Antonucci, speaking in front of more than 100 international experts at the Congress in Fulda, reported a response rate of about 80% observed treating autistic children with the Rerum® in the context of an integrated approach.

Conclusion

Although the etiology of autism still remains an unsolved puzzle with environmental and genetic factors playing a role that has not yet been fully established, it appears that strategies based on food supplements aiming at counteracting neuroinflammation and on the reconstitution of the gut and the brain microbiota may prove useful in the integrated approach to the disease [28, 29, 30]. With the invention and development of the Rerum®, a supplement that can be integrated in the context of reconstituting the gut and the brain microbiota [31], an additional option for natural immunotherapy becomes available.

Acknowledgements

The Author wishes to thank Dr. Stefania Pacini for her relentless support and insightful advice; Dr. Heinz Reinwald and Kerstin Reinwald for their contribution to the industrialization of Rerum® and for the organization of the Fourth International Congress on Integrative Medicine that was held in Fulda, Germany, on April 1 and 2, 2017.

Ethics

This article is original and contains unpublished material.

Conflict of interest

Marco Ruggiero, MD, PhD, is the inventor and the owner of the intellectual property of Rerum® that is licensed to dr. reinwald healthcare gmbh+co kg, Germany. Marco Ruggiero is the founder and CEO of the Swiss company Silver Spring Sagl, a company that produces and distributes foods and supplements; none of the products of this company is mentioned in this article. Marco Ruggiero is member of the Editorial Board of The Madridge Journal of Vaccines; he receives no remuneration for his editorial work.

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