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Review

The spectrum of post-vaccination inflammatory CNS demyelinating syndromes

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ABSTRACT

A wide variety of inflammatory diseases temporally associated with the administration of various vaccines, has been reported in the literature. A PubMed search from 1979 to 2013 revealed seventy one (71) documented cases. The most commonly reported vaccinations that were associated with CNS demyelinating diseases included influenza (21 cases), human papilloma virus (HPV) (9 cases), hepatitis A or B (8 cases), rabies (5 cases), measles (5 cases), rubella (5 cases), yellow fever (3 cases), anthrax (2 cases), meningococcus (2 cases) and tetanus (2 cases). The vast majority of post-vaccination CNS demyelinating syndromes, are related to influenza vaccination and this could be attributed to the high percentage of the population that received the vaccine during the H1N1 epidemic from 2009 to 2012. Usually the symptoms of the CNS demyelinating syndrome appear few days following the immunization (mean: 14.2 days) but there are cases where the clinical presentation was delayed (more than 3 weeks or even up to 5 months post-vaccination) (approximately a third of all the reported cases).

In terms of the clinical presentation and the affected CNS areas, there is a great diversity among the reported cases of post-vaccination acute demyelinating syndromes. Optic neuritis was the prominent clinical presentation in 38 cases, multifocal disseminated demyelination in 30, myelitis in 24 and encephalitis in 17. Interestingly in a rather high proportion of the patients (and especially following influenza and human papilloma virus vaccination-HPV) the dominant localizations of demyelination were the optic nerves and the myelon, presenting as optic neuritis and myelitis (with or without additional manifestations of ADEM), reminiscent to neuromyelitic optica (or, more generally, the NMO-spectrum of diseases). Seven patients suffered an NMO-like disease following HPV and we had two similar cases in our Center. One patient with post-vaccination ADEM, subsequently developed NMO.

Overall, the risk of a demyelinating CNS disease following vaccination, although non-negligible, is relatively low. The risk of onset or relapse of CNS demyelination following infections against which the vaccines are aimed to protect, is substantially higher and the benefits of vaccinations surpass the potential risks of CNS inflammation. This does not in any way exempt us from “learning” the lessons taught by the reported cases and searching new and safer ways to improve vaccination techniques and increase their safety profile.

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1. Introduction

1.1. Vaccinations and autoimmunity

The prevalence of autoimmunity has been continuously rising during the last decades, mainly in the “Western” world. Immune mediated diseases became nowadays one of the leading causes of morbidity and mortality worldwide [1–3]. A complex of genetic and environmental factors have been suggested as responsible [4,5], including various infections, toxins, and drugs that have been all shown to be linked with the onset or exacerbation of autoimmune conditions [6,7].

The more prominent increase of the prevalence of autoimmune diseases in the “Western” world may be also related to additional factors, such as pollution/accumulation of toxic substances, extensive usage of wireless networks, psychological stress and exaggerated use of antibiotics which cause an over-sterilized immunological milieu [8]. All of the above may contribute to an immune-dysregulation and disruption of the delicate networks/mechanisms that maintain self-tolerance, in genetically susceptible individuals, or may act as co-players in a complex interaction with various additional risk-factors.

Other environmental factors that may induce an immune “adjuvant” effect (boosting the immune response) include infectious agents and chemical substances such as silicone, alum and pristane, which are by themselves capable to induce autoimmunity in animal models [9–11].

Vaccines, which contain both attenuated infectious agents or their main immunogenic proteins and chemical adjuvants, represent one of most debatable and characteristic/unique paradigms of “environmentally”-induced trigger of autoimmunity. In this review we will summarize the worldwide experience, based on the published cases during the last 25 years, of central nervous system demyelinating diseases (acute disseminating encephalomyelitis—ADEM, multiple sclerosis—MS, myelitis, neuromyelitis optica—NMO and optic neuritis) associated with various vaccinations. The immunopathogenetic mechanisms involved will be discussed.

2. Vaccinations and CNS inflammatory diseases

A wide variety of inflammatory diseases temporally associated with the administration of various vaccines has been reported in the literature (Table 1). A PubMed search from 1979 to 2013 using the terms “vaccination/encephalitis”, “vaccination/encephalomyelitis”, “vaccination/ADEM”, and “optic neuritis/neuropathy/vaccination” revealed seventy one [71] cases within the above criteria (Table 2). The most commonly reported vaccinations that were associated with CNS demyelinating diseases included influenza (21 cases), human papilloma virus (HPV) (9 cases), Hepatitis A or B (8 cases), rabies (5 cases), measles (5 cases), rubella (5 cases), yellow fever (3 cases), anthrax (2 cases), meningococcus (2 cases) and tetanus (2 cases). As can be seen from Table 2, the vast majority of post-vaccination CNS demyelinating syndromes are related to influenza vaccination and this could be attributed to the high percentage of population that received the vaccine during the H1N1 epidemic from 2009 to 2012.

In terms of the clinical presentation and the affected CNS areas, there is a great diversity among the reported cases of post-vaccination acute demyelinating syndromes (Table 2). Optic neuritis was the prominent clinical presentation in 38 cases, multifocal disseminated demyelination in 30, myelitis in 24 and encephalitis in 17. Interestingly in a very high proportion of the patients (and especially following influenza

vaccination) the dominant localizations of demyelination were the optic nerves and the myelon, presenting as optic neuritis and myelitis (with or without additional manifestations of ADEM). This predisposition to the spinal cord and the optic nerves is reminiscent to neuromyelitic optica (or, more generally, the NMO-spectrum of diseases) that are highly associated with anti-aquaporin-4 antibodies. Indeed, as seen in Table 2, seven patients suffered an NMO-like disease following various vaccinations, especially HPV [12–14]. This raises the possibility of cross-reactivities between aquaporin epitopes and certain viral proteins and possibly, a link between ADEM and NMO. The latter is supported by case reports, such one patient with post-vaccination ADEM who subsequently developed NMO [15]. However, the incidence of anti-aquaporin antibodies in ADEM was low, as compared to anti-MOG antibodies [16].

Usually the symptoms of CNS demyelination appear few days following the immunization (mean: 14.2 days—Table 2) but there are cases in which the clinical presentation was delayed (more than 3 weeks or even up to 5 months post-vaccination) (approximately a third of all the reported cases—Table 2).

3. The spectrum of post-vaccination CNS demyelinating syndromes

3.1. Acute disseminated encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system (CNS) [17]. It is a rather rare disease with an incidence of 0.6 to 0.8 per 100,000 per year [18–20]. ADEM can occur in any age but is mainly a disease of children and young adults with a mean age of onset of 5–6 years [21–23] and a higher incidence in males [19]. The clinical presentation of ADEM is widely variable, depending on the distribution of lesions in the CNS. Encephalopathy, occurring in up to 74% of patients [24], is considered mandatory for definite diagnosis. Other neurological signs include pyramidal syndrome, cranial nerve palsies, ataxia, seizures, optic neuritis and speech impairment. ADEM is defined (according to the criteria proposed from the International MS Group [17]) as a first ever clinical event with presumed inflammatory or demyelinating cause, with an acute or subacute onset, that affects multifocal areas of the CNS and is usually polysymptomatic and includes encephalopathy (i.e., behavioral change or altered level of consciousness). Additional criteria include: the presence of focal/multifocal lesion(s) predominantly affecting the white (but also the gray) matter without evidence of previous destructive white matter changes, the occurrence of clinical/radiologic improvement (although there may be residual deficits), and the absence of other etiology that could explain the event.

ADEM has a monophasic course in the majority of patients; if relapse occurs, it usually happens within 3 months from its onset. However, cases with relapse with symptoms different than the original ones have been reported and are defined as recurrent (RADEM) or multiphasic disseminated encephalomyelitis (MDEM) [23,25–33]. The existence of such forms of ADEM remains controversial.

Differentiation between ADEM, multiple sclerosis (MS), is still a challenge [21], especially in the case of relapsing ADEM, where the border between ADEM and MS is more obscure. The lack of oligoclonal antibodies and the high cellularity of the CSF, the involvement of CNS gray matter, and the presence of fever, confusion and headache are some of the main differentiating features between ADEM and MS [18,24,34]. Histopathologically, focal, perivenous and subependymal

Table 1
The spectrum of post-vaccination CNS demyelinating diseases.

ADEM	References: [18,52,135–137,139,141,142,145–148,150–155,158,160,163–166,169–173]
Encephalitis with white matter involvement	References: [135,137,139,140,143,146,147,150,151,153,157,158,160,161,165,171,172]
Myelitis	References: [12–14,52,134,137–139,141,142,144,148,159,161,162,167–169,172]
Optic neuritis	References: [12–14,18,62–77,79,139,145,148,149,151,153,154,156,168,170,173]
NMO-spectrum	References: [12–14,52,148,162,168]

changes (at the early period, mainly T cell infiltrates, accompanied by few plasma cells and later microglial infiltrates) dominate the histopathological pattern of ADEM, leading to the formation of disseminated masses or conglomerates. Despite the predisposition for the white matter, the cortical and deep gray matter (frequently the thalamus) is affected and this further differentiates ADEM from MS. In the long term, only a sparse gliosis can be detected without significant myelin loss in ADEM [18].

The current pathogenetic hypothesis in post-vaccination ADEM is that antigens of viral origin cross-react with myelin components (molecular mimicry) and in a secondary manner induce a hyperergic reaction, that leads to the development of disseminated demyelination. Myelin proteins have shown resemblance to several viral sequences and anti-MBP antibodies have indeed been detected following vaccination with Semple rabies vaccine [35,36]. Another hypothesis is that vaccination may activate in a non-specific way distinct clones of anti-myelin T-cells and that suppressor or regulatory cells that are aimed to control this abnormal reactivity are compromised or malfunctioning.

Post-vaccination ADEM accounts for 5–10% of all cases [18,34]. However, despite a close temporal relation to vaccinations, there is no concrete evidence of a clear pathogenetic correlation. The incidence of post-vaccination ADEM has largely fluctuated over the last decades with a peak occurring between 1927 and 1929 and also –seemingly during the last years. This can be probably related to the methods used for vaccine production, the amount of myelin antigens included and –most importantly– the type of the used adjuvant. The overall incidence of post-vaccination ADEM is estimated to 0.1–0.2 per 100,000 and the higher risk has been reported following immunization against measles. Other common causes of post-vaccination ADEM include vaccines against the varicella zoster, the rubella, the smallpox and the influenza viruses [18]. On the other hand, surprisingly, certain vaccines such as anti-tetanus vaccination were shown to have a negative correlation with ADEM (statistically significant decreased risk) [37].

Vaccination against Hepatitis B is one of the most controversial possible causes of demyelinating disease. An increased risk for ADEM was suggested by Touze et al. [38,39] and Mikaeloff et al. reported a slight increase of the incidence of CNS demyelinating diseases specifically following Engerix B vaccine [40]. For the present, there is no convincing proof of a causative correlation between HBV and ADEM/MS or other acute demyelinating diseases [41–45]. Analysis of the existing data argues against such causal relationship and indicates that the benefits of the vaccine clearly surpass the potential risks of CNS inflammation [46].

Gardasil vaccination is a novel type of vaccine targeting the human papilloma virus that has been shown to be efficient for the prevention of cervical, vulval and vaginal dysplasia and cervical cancer [47–49]. Only few cases of post-vaccination ADEM have been reported in the literature (Table 2).

Post-vaccination ADEM is usually observed after primary vaccination and much less following revaccination [18], but there are reports where a relapse, or a second neurological event was observed after repeated immunizations with the same virus [12–14]. Noteworthy, there is a substantial percentage of the reported post-vaccination cases that subsequently developed MS (Table 2) [46,50–52].

3.2. Isolated optic neuritis

Optic neuritis (ON) is an inflammatory demyelinating condition of the optic nerve. Most cases are idiopathic or associated with ADEM or MS. ON is the most common acute optic neuropathy in young adults with an incidence of 1–3 per 100,000 population per year [53–59].

Acute ON usually presents as an isolated clinical event without additional neurological involvement (monosymptomatic ON) [60]. Clinical features include periorcular pain, abnormal visual acuity and visual field defects, reduced color vision, a relative afferent pupillary defect, and abnormal visual evoked potentials. The fundus appears normal but occasionally edema of the optic nerve head (papillitis) is observed

[60]. MRI white matter abnormalities identical to those seen in MS can be found in half of the monosymptomatic ON cases [61]. The visual deficits peak over 1 to 2 weeks and usually substantially improve over the following month. However, many patients continue to have residual visual dysfunction, even when visual acuity improves ad integrum.

Optic neuritis represents a unique paradigm of an association of vaccines with demyelination. There are numerous reports of isolated (either unilateral or bilateral) optic neuritis following various types of vaccinations against infectious agents [62], including measles [63–65], anthrax [66], rubella [63–65], Hepatitis A and B [67–69], influenza [70–75], pneumococcal vaccine [12], meningococcal vaccine [76], rabies [77,78] and BCG [79]. As shown in Table 2, the most often demyelinating clinical presentation associated with vaccinations is optic neuritis, accounting for more than half of the reported cases in the literature.

3.3. Multiple sclerosis

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) that is characterized by loss of motor and sensory function, caused by immune-mediated inflammation, demyelination and subsequent axonal damage [80–82]. MS could be considered as the chronic form of ADEM and ADEM can sometimes develop to MS, as mentioned above.

Clinically, most MS patients experience recurrent episodes (relapses) of neurological impairment but eventually in most of the cases the course of the disease becomes chronic and progressive with time, leading to accumulating motor disability, and cognitive deficits.

Histologically, perivenular inflammatory lesions (consisting of mononuclear infiltrations) are evident in the earlier phases of the disease, resulting in demyelinating plaques, the pathological hallmark of MS [81]. Inflammation leads to damage of oligodendrocytes and demyelination causes disruption of the conduction of neuronal signals in the affected regions. As the disease progresses disability and neuronal damage [83] become permanent and irreversible.

The inflammatory process in MS is propagated by an autoimmune cascade, involving mainly T-cells that target myelin self antigens [84,85], possibly mediated by mechanisms of molecular mimicry (cross-reactive antigens expressed by viruses or other microorganisms and myelin components) [86]. An alternative hypothesis is that “naturally” existing myelin-specific T-cells, especially of the Th17 phenotype, may expand to critical pathogenic quantities [87] due to malfunctioning immunoregulatory mechanisms (such as those involving the Th2, Th3, Tr1, Treg, and CD8+ T-cells).

Additionally, environmental, genetic and infectious factors seem to play important roles in MS pathogenesis, similarly to autoimmunity in general. MS is not a homogenous disease and several distinct immunopathological profiles of the disease exist, including forms in which humoral immune mechanisms are prominent [88]. Indeed, increased B-cell numbers, mainly memory cells and short-lived plasmablasts can be detected in the CNS of MS patients [89]. Plasmablasts persist in the cerebrospinal fluid (CSF) and their number correlates with the intrathecal IgG synthesis (evidenced by the presence of oligoclonal antibodies in the CSF, one of the hallmarks of MS diagnosis) [89,90]. Moreover, B cells, plasma cells, autoantibodies and complement have been detected in MS lesions [91,92]. Recently, ectopic lymphoid follicles have been found in the CNS of patients with MS [93,94], especially in those with progressive disease.

Numerous studies have shown that the risk of MS relapse is increased by infections (approximately twofold [95]), accompanied by enhanced lesion activity in the MRI [96]. Moreover, relapses associated with an infection seem to cause more neurological dysfunction [95].

Vaccinations have been also incriminated/implicated as triggers of the onset of MS in susceptible individuals [97]. Some studies [28,37,98] indicated a significant risk for CIS or conversion to clinically

Table 2

A list of case reports with various post-vaccination CNS demyelinating syndromes, published in the literature.

	Type of vaccine	Age/ gender	Onset time post-vaccination	Clinical syndrome					Response to treatment and outcome	Reference
				ADEM	Encephalitis	Myelitis	Optic neuritis	NMO		
1	Influenza	70/M	7 days			+			Partial recovery after steroids + PE	Nakamura et al. [134]
2	Influenza	62/M	5 days			+			Partial recovery after steroids + PE in the second	Nakamura et al. [134]
3	Influenza	75/F	3 weeks	+	+				No response to PE and steroids; death	Shoamanesh and Traboulee [135]
4	Influenza	61/M	3 weeks, 3 months	+			+		IVMP: full recovery except 50% reduction of visual acuity	Huynh et al. [18]
5	Influenza	6/M	16 days	+					Steroids treatment/resolved	Iyoda et al. [136]
6	Influenza	83/F	8 days	+	+	+			Dramatic response to PE; died later of pneumonia	Machicado et al. [137]
7	Influenza	61/M	2 weeks			+			I.v. steroids and IVIG; full recovery	Ravaglia et al. [138]
8	Influenza	60/F	10 days			+			I.v. steroids and IVIG; full recovery	Ravaglia et al. [138]
9	Influenza	NA	NA	+	+	+	+		Recovery after i.v. steroids	Vilain et al. [139]
10	Influenza	59/F	2 weeks				+			Hull and Bates [71]
11	Influenza	61/F	NA				+		Good recovery following steroids	Ray and Dreizin [74]
12	Influenza	NA	NA				+		Recovery after steroids	Perry et al. [73]
13	Influenza	62/F	15 days				+		Improvement with steroids	Laffon-Pioger et al. [72]
14	Influenza type A + B	18/M	2 weeks				+		Recovery after steroids	Rubinov et al. [75]
15	Influenza (LAIV) as nasal flu vaccine	13/M	NA				+		Recovery after steroids	Crawford et al. [70]
16	H1N1 influenza	2/M	25 days		+				Full recovery after steroids treatment	Fujii et al. [140]
17	H1N1 influenza	33/F	15 days	(+)		+			Improvement with steroids	Maeda and Idehara [141]
18	H1N1 influenza	36/M	10 days	+		(+)			Marked improvement with steroids	Hoshino et al. [142]
19	H1N1 influenza	34/M	5 days		+				Complete recovery with steroids	Lee et al. [143]
20	H1N1 influenza	NA/F	4 days			+			Improved without treatment	Arcondo et al. [144]
21	H1N1 influenza	2/M	4 days; 6 days						Full recovery after steroids	Lapphra et al. [145]
22	Rabies	31/M	5 months	+	(+)				Paresis resolved; persisting neurological signs: seizures, behavioral changes	Gamboa et al. [146]
23	Rabies	24/M	1 week	+	+				Died after 37 years of encephalopathy; demyelinating lesions in pathology	Iizuka et al. [147]
24	Rabies	45/M	14 days	+		+		+	Improvement with steroids	Kulkarni, et al. [148]
25	Rabies	15/M	25 days					+		Gupta et al. [149]
26	Rabies	NA	NA					+		Dadeya et al. [77]
27	Polyvaccination	27/M	10 days	+	+				Death (day 21)	Labauge et al. [150]
28	Early summer encephalitis	36/M	After repeated immunization	+	+		+		Partial improvement	Schattenfroh [151]
29	Group A + C meningococcal vaccine	25/F	NA	+					Fast disappearance of symptoms and gradual resolution of lesions in MRI after i.v. MP	Py and Andre [152]
30	Meningococcal C	13/M	NA				+			Laria et al. [76]
31	Pneumococcal polysaccharide	87/M	Few days			+	+	+	Improvement of vision but not of quadriparesis with steroids	Kitazawa et al., Intern Med, 2012 [12]
32	Hepatitis B	40/M	6 weeks	+	+		+		Partially resolved after steroids	Cabrera-Gomez et al. [153]
33	Hepatitis B	39/F	4 weeks after the 2nd dose	+			+		Craniotomy and dexamethasone; residual dyslexia hemianopsia; resolution of the MRI lesions, except a porencephalic cyst	Konstantinou et al. [154]
34	Hepatitis A	23/F	3–7 days	+					Improvement of CNS signs with steroids but not of axonal neuropathy	Huber et al. [155]
35	Hepatitis A	39/M	6 days				+		Partial recovery after steroids	Huang et al. [69]

36	Hepatitis B	28/M	10 days						+		Albitar et al. [67]
37	Hepatitis B	9/F	7 days						+	Recovery after steroids	Erguven et al. [68]
38	Hepatitis and rabies	40/M	NA						+	Improvement with steroids	van de Geijn et al. [62]
39	Hepatitis B and polio	NA	NA						+		Stewart et al. [156]
40	Lyssa	NA	10 days						+	Died 3 days later; demyelinating lesions in CNS and optic nerves	Varga et al. [157]
41	Measles	7/M	3 days	+	+					Complete resolution of lesions within 2 weeks	Shu et al. [158]
42	Measles	19/F	4 days						+	Recovery after pulses of steroids	Hamano et al. [159]
43	Measles	13/M	3 weeks						+		Stevenson et al. [65]
44	Measles	15/M	Few hours						+	Good improvement with steroids	Moradian and Ahmadiéh [63]
45	Measles, rubella	16/M	Few hours						+		Arshi et al. [64]
46	Diphtheria, tetanus toxoid, whole cell pertussis	6/M	6 days	+	+					Recovery without treatment	Aydin et al. [160]
47	Yellow fever	53/M	NA						+	Death	Kengsakul et al. [161]
48	Yellow fever	56/M	45 days						+	Symptoms improved 5 days later	Chaves et al. [162]
49	Yellow fever	NA		+						NA	Miravalle et al. [163]
50	Smallpox, typhoid, polio, anthrax doses 1–2	19/M	12 days, 17 days, 17 and 5 days	+						Full recovery with IVIG, steroids and vaccinia immunoglobulin	Van Dam et al. [164]
51	Smallpox	30/M	10 days	+	+					Neurologic sequelae still present 1 year after	Sejvar, et al. [165]
52	Tetanus	NA	NA	+						Recovery without steroids	Hamidon and Raymond [166]
53	Tetanus	28/F	15 days						+	Steroids; partial resolution	Cisse et al. [167]
54	Rubella	31/F	5 days						+	Partial recovery with steroids	Kline et al. [168]
55	Rubella	14/M	16 days	+					+	Rapid improvement with steroids	Tsuru et al. [169]
56	Rubella	23/F	13 days						+		Stevenson et al. [65]
57	Rubella	17/M	Few hours						+	Recovery	Moradian and Ahmadiéh [63]
58	Japanese encephalitis	15/M	3 weeks						+	Recovery after steroids	Furukawa et al. [13]
59	Diphtheria/tetanus/poliomyelitis	7/M	NA	+					+	Full recovery	Mancini et al. [170]
60	Anthrax	39/M	1 month						+	Excellent recovery	Kerrison et al. [66]
61	Anthrax	23/M	2 weeks						+	Improvement with immunosuppression	Kerrison et al. [66]
62	BCG	12/F	5 days						+	Recovery	Yen and Liu [79]
63	HPV	20/F	28 days after second immunization	+	+					Relapsed twice after steroids cessation, required immunosuppression	Wildemann et al. [171]
64	HPV	15/F	23 days after second immunization	+	+	+				Neurological recovery and resolution of lesions after steroid treatment	Schaffer et al. [172]
65	HPV	17/F	4 months after the 3rd dose						+	Partial improvement with steroids, PE and Rituximab. At 5 months: still paraparesis and ON.	Menge et al. [14]
66	HPV	14/F	4 months post-3rd dose						+	Steroids, Rituximab, mycophenolate; stopped recurrences	Menge et al. [14]
67	HPV	13/F	Post-2nd immunization, time unknown						+	No response to steroids and PE; Rituximab started	Menge et al. [14]
68	HPV	18/F	5 months after 2nd immunization						+	NA	Menge et al. [14]
69	HPV	16/F	10 days post-2nd immunization	+					+	No further demyelinating events within 18 months follow-up. Patient remained with severe visual loss	DiMario et al. [173]
70	HPV	16/F	21 days post-3rd immunization	+					+	NA	Sutton et al. [52]
71	HPV	25/F	16 days post-2nd immunization	+						4 months later, the patient suffered from a second event and MRI showed a new lesion (diagnosed then as CDMS)	Sutton et al. [52]

definite MS (CDMS) following Hepatitis B (HBV) immunization, whereas other investigators did not confirm this observation [99]. A recent extensive review from the US Institute of Medicine did not find sufficient evidence to support a causal relationship between the onset of MS and various common vaccinations (measles, mumps and rubella, influenza, Hepatitis A, Hepatitis B, human papilloma virus (HPV), diphtheria, tetanus, acellular pertussis, or meningococcus) [100]. Furthermore, pooled analyses found no evidence that vaccination against tuberculosis (BCG), or against Hepatitis B, influenza, measles, typhoid fever, diphtheria or tetanus, was associated with an increased risk of developing MS [101].

Vaccinations have been also linked to the occurrence of relapses of MS [50]. Deterioration or exacerbation of MS has been described in association with several vaccines [summarized by Loebermann et al. [51]] including lately human papilloma virus vaccination for protection against gynecological cancers [46,52]. In some studies, this increase was impressive; for instance a ten-fold increase of relapse risk and higher MRI activity were reported in the 3 months following vaccination for yellow fever [102].

However, Confavreux et al. [103] in a European database study that evaluated a total of 653 MS relapses showed that of all the patients with a relapse, only 2.3% had been vaccinated during the preceding two-month risk period as compared with 2.8 to 4.0% during the control periods. The relative risk of relapse associated with exposure to any vaccination during the previous two months was 0.71. In any case, the risk of a relapse following the infection itself seems to be much higher than the risk imposed in vaccination. De Keyser et al. reported an overall risk of relapse of 30% in patients suffering an influenza infection as compared to only 5% following vaccination against influenza [104].

3.4. Myelitis

Inflammatory diseases of the spinal cord are collectively described as myelitis. Myelitis can be either infectious or immune mediated (autoimmune). It can be classified according to the areas of the spinal cord affected as [105,106]:

- i. *transverse myelitis* (affecting one or two segments and predominantly the white matter of the cord—it can involve the whole width of the cord or half of it),
- ii. *long extensive myelitis (LETM)*, which affects most of the width of the cord at more than three consequent segments
- iii. *poliomyelitis*, that affects multiple areas of the gray matter of the cord (the anterior horns),
- iv. *myeloradiculitis*, that affects both the white matter of the cord and the roots.

In terms of the causative factors, the most common type of myelitis worldwide is infectious myelitis, either caused by viruses (polio virus, HTLV-1, EBV, CMV, HSV), by bacteria (such as, *Borrelia burgdorferi* – Lyme's disease–, in Europe and North America and *Brucella*, especially in less developed areas of the world where milk is not pasteurized), by mycoplasma infection and by parasites such as schistosoma. During the last decade, HIV-associated myelitis has emerged, especially in the HIV-endemic areas in Africa.

Immune mediated myelitis propagated by autoimmune mechanisms attacking mainly the white matter of the spinal cord is usually presented as *acute transverse myelitis (TM)* [105,106], which may be idiopathic (isolated or as a part of ADEM/MS), post-infectious or post-vaccination. TM is characterized by inflammation and demyelination across both sides of one level, or segment, of the spinal cord resulting in symptoms of neurological disconnection and dysfunction below the level of the demyelinating area [106]. Myelitis can be also one of the hallmarks of neuromyelitis optica (NMO) (see next section).

As shown in Table 2, in 24 out of the 71 reported cases in our review, one of the major presentations of the CNS demyelinating syndrome was

myelitis, including 7 cases that met the criteria of NMO-spectrum of diseases.

3.5. Neuromyelitis optica

Neuromyelitis optica (NMO), also known as Devic's disease, is an idiopathic, severe, demyelinating disease of the central nervous system that preferentially affects the optic nerve and spinal cord. NMO has long been thought to be a variant of multiple sclerosis (MS) but it can be clearly distinguished from MS by clinical, neuroradiological, and pathological criteria and the presence of the highly specific serum autoantibodies, against the water channel aquaporin-4 [107–109] in ~75% of NMO patients [107–112]. However, the exact role of antibodies against AQP4 in the pathogenesis of the disease is not clear.

Among all the reported cases with post-vaccination CNS demyelinating syndromes, there were 7 cases with NMO spectrum of diseases (Table 2). Interestingly, in most of these cases the vaccine involved was Gardasil against human papilloma virus, raising the possibility of cross-reactivity between the used viral antigens and aquaporin-4. As expected, the dominant presentation included optic neuritis and/or myelitis with longitudinal spinal lesions [14]. Interestingly, in most of these cases, there was a high incidence of recurrence (second event of demyelination/neurological signs few days up to months following the vaccination).

4. Discussion

Vaccines are one of the greatest achievements of modern medicine and are commonly and safely administered to humans worldwide. However, in rare occasions, vaccines can give rise to enigmatic inflammatory conditions [40,113] and even cause overt autoimmune diseases, by inducing the production of autoantibodies [113], or by breaking the mechanisms of self-tolerance. These rare events are usually documented within weeks following vaccination [40,114] (Table 2), making difficult if not impossible to delineate a causal relationship between vaccination and autoimmune disease. Nevertheless, for some vaccines such a causal link seems very logical. In 1976 an outbreak of Guillain-Barré syndrome (GBS) followed immunization with the “swine flu” vaccine [115,116]. Similar causal relationship has been shown in transverse myelitis (after oral polio vaccine), in arthritis (following diphtheria–tetanus–pertussis and measles–mumps–rubella vaccine) and in autoimmune thrombocytopenia (after measles–mumps–rubella vaccine) [113].

In addition, a number of animal models enabled a better way of studying the link between vaccines and autoimmunity. Immunization of dogs induced the production of 9 different autoantibodies including lupus-associated ones [117] and vaccination of diabetic prone newborn animals was associated with an increased occurrence of diabetes mellitus [118]. Intra-peritoneal immunization of salmon fish with vaccines embedded in oil-adjuvants also induced autoantibodies and the outbreak of granulomatous disease of the liver and peritoneum and immune mediated glomerulonephritis [119].

Specifically, regarding vaccination-induced autoimmunity of the central nervous system (CNS), application of unpurified rubies vaccine (which contained fragments of myelin with antigenic properties) [18] was shown to induce encephalomyelitis/ADEM, resembling the induction methods of experimental autoimmune encephalomyelitis (EAE) in animals, through immunization with myelin antigens in adjuvant [120–122].

A striking clinical example of post-vaccination CNS inflammatory disease is that of development of ADEM in Alzheimer patients, following administration of an experimental vaccine that contained aggregates of synthetic A β 42 fragments of amyloid precursor protein [123,124]. In experimental animals, a similar EAE/ADEM disease was induced with A β 42 vaccination, but only when the vaccine included complete Freund's adjuvant. The latter observation underlines the importance and central

role of adjuvants in induction of ADEM and of autoimmunity in general [125,126].

The pathogenic role of adjuvants in the induction of autoimmune syndromes has been highlighted by Yehuda Shoenfeld who introduced the term ASIA syndrome (autoimmune syndromes in association with adjuvants) [125,126]. In general, immunologic adjuvants are substances that enhance the antigen-specific immune responses [127] and are therefore commonly used in vaccines. Eventually, the efficacy of most vaccines depends on the presence of an adjuvant in conjunction with the infectious antigen [128].

The effects of the adjuvants are accomplished via several mechanisms that affect both the innate and the adaptive immune systems. Adjuvants mimic evolutionarily conserved molecules (e.g. bacterial cell walls, LPS, unmethylated CpG-DNA) and bind to Toll-like receptors (TLRs). They activate dendritic cells (DCs), lymphocytes and macrophages, increasing subsequently the release of chemokines and cytokines from T-helper and mast cells [9,129–131].

Currently the most widely used adjuvant in medicine is aluminium. Aluminium interferes with lysosomal functions and stimulates the production and secretion of cytokines such as IL-1b; IL-18 and IL-33 [128,131]. Adjuvants also provide physical protection to antigens, enabling thus a longer exposure of the immune system to the antigen, and a more robust (B-cell and T-cell) response. Adjuvants were thought to carry little risks, but several animal and human studies have demonstrated the ability of some of them to inflict an autoimmune process, such as in the case of Tetramethylpentadecane (TMPD—pristine), which was shown to induce a lupus-like disease in mice [132,133].

Adjuvants present in the vaccines can induce a non-specific activation of the immune system with a subsequent expansion of autoreactive (in our case, myelin specific) lymphocytes that may be further accelerated by defective regulatory cells/circuits, in genetically susceptible individuals.

Molecular mimicry i.e. the molecular similarity between the proteins of the viruses used for the vaccination and self antigens (for instance, CNS myelin components) also represents one of the main immunopathogenetic mechanisms in post-vaccination CNS demyelination [125–127].

In addition to the central role of adjuvants and molecular mimicry in the pathogenesis of post-vaccination systemic or CNS autoimmunity, other vaccine-related factors may also significantly contribute to the outbreak of an autoimmune response, including the type and dose of the infectious agent, the degree of its attenuation (live attenuated or dead) and the way of administration. It is theoretically possible that vaccines administered parenterally and not via the “natural” way of infection could carry a greater risk for induction of an autoimmune reaction, bypassing the control mechanisms of self tolerance.

In conclusion, the risk of a demyelinating CNS disease following vaccination, although non-negligible, is relatively low. From the existing data it seems that the risk of onset or relapse of CNS demyelination following infections against which the vaccines are aimed to protect is substantially higher.

Analysis of the existing data from epidemiological studies argues against a clear causal relationship between vaccines in general, and MS or other demyelinating diseases and advocates in favor of the benefits of vaccinations versus the potential risks of CNS inflammation/demyelination. This does not in any way exempt us from “learning” the lessons taught by the reported cases and searching new and safer ways to improve vaccination techniques and increase their safety profile.

Take-home messages

- Central nervous system (CNS) myelin can be often the target of an autoimmune process that follows various vaccinations and leads to a wide spectrum of immune mediated demyelinating syndromes.
- ADEM is the prototype (and most extensively described) white matter disease associated with vaccines. Other common syndromes include

acute optic neuritis (the commonest post-vaccination isolated CNS syndrome reported in the literature) and acute transverse myelitis, but also the onset and/or exacerbation of a chronic disease such as multiple sclerosis (MS) or neuromyelitis optica (NMO) has been frequently reported, following various vaccinations.

- The most common vaccines that are reportedly associated with CNS demyelinating diseases in the literature are influenza vaccines (by far the highest number of reported cases) and human papilloma virus (HPV) vaccination. Other vaccines that have been associated with a spectrum of CNS demyelinating diseases include Hepatitis A or B, rabies, measles, rubella, yellow fever, anthrax, meningococcus and tetanus vaccines. The high number of reported post-vaccination CNS demyelinating syndromes related to influenza vaccination could be attributed to the high percentage of population that received the vaccine during the H1N1 epidemic from 2009 to 2012.
- There is no absolute way to definitely link the onset or exacerbation of demyelination with the vaccine, but the close temporal association with the time of vaccination strongly argues in favor of such pathogenetic correlation.
- Usually the CNS demyelinating syndrome appears shortly (during the 3–4 weeks following the vaccination) but there are reports of longer time intervals of up to 6 months.
- Immune adjuvants that are included in the vaccine preparations and aim to enhance the immune responses have been incriminated as one of the main mechanisms responsible for the immunopathogenesis of these syndromes (“ASIA” spectrum of diseases).
- Molecular mimicry i.e. the molecular similarity between the proteins of the viruses used for the vaccination and self antigens (CNS myelin components) represents the second main immunopathogenetic mechanisms in post-vaccination CNS demyelination.
- Other vaccine-related factors that may also significantly contribute to the outbreak of an autoimmune response include the type and dose of the infectious agent, the degree of its attenuation (live attenuated or dead) and the way of administration.
- Environmental and host genetic factors seem to play an important role.
- The overall risk of a demyelinating CNS disease following vaccination, although non-negligible, is relatively low (estimated to around 0.1%) and the risk of onset or relapse of CNS demyelination following infections against which the vaccines are aimed to protect is substantially higher.
- The existing epidemiological data indicate that the benefits of vaccinations clearly prevail over the potential risks of CNS inflammation/demyelination.
- This, of course, does not in any way exempt us from “learning” the lessons taught by the reported cases and searching new and safer ways to improve vaccination techniques and increase their safety profile.

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