Vaccine 32 (2014) 5893–5900

Contents lists available at ScienceDirect

Vaccine

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

Vaccination recommendations for patients with neuromuscular disease

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ARTICLE INFO

Article history:
Received 10 July 2014
Received in revised form 28 August 2014
Accepted 2 September 2014
Available online 16 September 2014

Keywords:
Chronic disease
Immunocompromised patients
Influenza vaccination
Neurologic disease
Neuromuscular disease
Pneumococcal vaccine

ABSTRACT

Neuromuscular diseases (NMDs) encompass a broad spectrum of conditions. Because infections may be relevant to the final prognosis of most NMDs, vaccination appears to be the simplest and most effective solution for protecting NMD patients from vaccine-preventable infections. However, very few studies have evaluated the immunogenicity, safety, tolerability, and efficacy of different vaccines in NMD patients; therefore, detailed vaccination recommendations for NMD patients are not available. Here, we present vaccination recommendations from a group of Italian Scientific Societies for optimal disease prevention in NMD patients that maintain high safety levels. We found that NMD patients can be classified into two groups according to immune function: patients with normal immunity and patients who are immunocompromised, including those who intermittently or continuously take immunosuppressive therapy. Patients with normal immunity and do not take immunosuppressive therapy can be vaccinated as healthy subjects. In contrast, immunocompromised patients, including those who take immunosuppressive therapy, should receive all inactivated vaccines as well as influenza and pneumococcal vaccines; these patients should not be administered live attenuated vaccines. In all cases, the efficacy and long-term persistence of immunity from vaccination in NMD patients can be lower than in normal subjects. Household contacts of immunocompromised NMD patients should also be vaccinated appropriately.

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http://dx.doi.org/10.1016/j.vaccine.2014.09.003
0264-410X/

1. Introduction

Neuromuscular diseases (NMDs) encompass a broad spectrum of conditions that include spinal muscular atrophy, congenital myopathies, myasthenia gravis, limb-girdle muscular dystrophies, polymyositis, dermatomyositis, and other less common muscular dystrophies [1–4]. NMD pathogenesis, incidence, clinical presentation, and outcome significantly differ from disease to disease; however, most NMDs are thought to share a common increased risk of infections [1–4]. Because infections may be relevant to the final prognosis of most NMDs, vaccination appears to be the simplest and most effective solution for protecting NMD patients from vaccine-preventable infections [5]. Thus, NMDs have been systematically listed as clinical conditions for which vaccines are strongly recommended [5,6]. However, very few studies have evaluated the immunogenicity, safety, tolerability, and efficacy of different vaccines in NMD patients; therefore, detailed vaccination recommendations for NMD patients are not available. Current recommendations group all NMDs without considering disease-specific factors that might influence vaccine activity and immunization schedules. Furthermore, national immunization recommendations for patients with autoimmune diseases, including some NMDs, are significantly different between Europe, North America, and Australia, highlighting the lack of evidence-based data [7]. Data on vaccination rates in NMD patients are sparse and not conclusive. However, as with other chronic conditions that lack detailed and uniform vaccination recommendations, it is highly probable that most NMD patients are not adequately vaccinated [5,8]. Physicians and NMD patients or guardians may refuse vaccinations due to uncertainties about the clinical efficacy, safety, and tolerability of vaccines [9]. This contributes to reduced vaccine coverage and poor protection of those patients who would benefit the most from vaccinations. Here, we present vaccination recommendations from a group of Italian Scientific Societies for optimal disease prevention in NMD patients that maintain high safety levels.

2. The risk of infections in NMD patients

Few studies have evaluated the potential association between NMDs and increased risk of infections. In most cases, these studies have assessed the risk of influenza and other respiratory infections among children and show that NMDs are significantly associated with complications related to these infections. In a retrospective cohort study, patients aged 21 years or younger who were hospitalized with community-acquired laboratory-confirmed influenza and had NMDs were more likely to have severe disease that required mechanical ventilation, and their risk of respiratory failure was 12% [10]. In a similar study of children hospitalized for influenza, NMDs and cardiac diseases were the only underlying conditions that were independent risk factors for prolonged hospitalization [11]. Children with NMDs have also been shown to be at an increased risk of severe respiratory syncytial virus (RSV) disease [12]. Another study also reported that children with NMDs had the same risk of developing severe respiratory problems when infected by RSV as patients with bronchopulmonary dysplasia [13], a known risk factor of complicated respiratory infections. In adults, one study found that up to 37.3% of NMD patients with polymyositis or dermatomyositis developed infectious complications, including pyogenic, non-pyogenic, and opportunistic infections [14]. The pyogenic infections in this study were mainly due to aspiration pneumonia with *Streptococcus pneumoniae* and calcinosis cutis infection. A large variety of microorganisms, mainly *Pneumocystis jiroveci* and *Candida albicans*, have also been found responsible for opportunistic infections [15].

The best understanding of the risk of infection-related complications in NMD patients comes from clinical experience or from the evaluation of more common diseases that are associated with similar pathogenesis, clinical conditions, and therapy. Several NMDs are autoimmune, and some evidence suggests that humoral and cellular immune responses could contribute to the pathological processes of others. These processes include the invasion of necrotic muscle fibers by macrophages and cytotoxic T-cells, complement activation resulting in the deposition of membrane attack complexes on necrotic fibers, and the expression of HLA class I antigens on dystrophic muscle fibers [16,17]. These NMD patients are treated with immunosuppressive drugs [4,18]. Patients with Duchenne- and Becker-type muscular dystrophies, myasthenia gravis, some cases of limb girdle muscular dystrophy types 2C, 2D, 2E, and 2F, multiple sclerosis, polymyositis, dermatomyositis, and inclusion body myositis are among those treated with immunosuppressive drugs (Table 1). Corticosteroids (CS) are the most common immunosuppressive agents prescribed for patients with immune disorders. CS administration, particularly at the highest recommended dosages and for long periods of time, is associated with an increased risk of developing several infections [19]. This has been demonstrated by several studies in patients with diseases other than NMD [5,9], and the results of these studies remain useful for NMD patients who receive similar treatment. In a case-control analysis, adults with rheumatoid arthritis (RA) who used 5 mg prednisolone had a 30%, 46%, or 100% higher risk of serious infection when prednisolone was used continuously for 3 months, 6 months, or 3 years, respectively [20]. The risk associated with 5 mg prednisolone for 3 years was similar to that associated with 30 mg prednisolone for one month. Discontinuing a 2-year course of 10 mg prednisolone in the previous 6 months halved this risk of serious infection [20]. The use of anti-tumor necrosis factor (TNF) α for autoimmune diseases also contributes to a higher risk of infection in these patients. Common infections, such as upper respiratory tract infections, are frequent adverse events and reasons for discontinuing anti-TNFα therapy in clinical trials and observational studies [21]. Moreover, anti-TNFα therapy has been associated with serious infections due to *S. pneumoniae*, including severe pneumonia, necrotizing fasciitis, and fatal septicemia [21,22] and with the development of tuberculosis and opportunistic infections due to dysregulated Th1 responses [23,24]. Anti-TNFα in addition to disease modifying anti-rheumatic drugs (DMARDs) treatment in patients with RA or spondyloarthropathy doubled the infection incidence rate ratio compared to DMARDs alone, while anti-TNFα-in addition to-CS tripled the infection incidence rate ratio [25].

Most NMD patients experience a progressive reduction in respiratory muscle strength (Table 1) [26–28]. When respiratory muscle strength is 25–30% of normal, airflow is significant limited, and adequate coughing occurs. Furthermore, the lungs have reduced functional residual capacity, which increases the work needed to breathe, alters the ventilation/perfusion relationship, and results in less efficient gas exchange. Scoliosis due to decreased muscle support, reduction in spontaneous movement, and swallowing dysfunction leads to aspiration and a high prevalence of gastroesophageal reflux, both of which worsen respiratory conditions. Hypopnoea, oxygen desaturation, and hypercapnia are also common. Once the respiratory reserve is compromised, any increase in the respiratory load can lead to respiratory failure, and mild to moderate respiratory infections become severe. Poor coughing (i.e., difficulty in clearing secretions) is associated with recurrent bacterial infections that can cause bronchiectasis and parenchymal damage to the lungs [26–28]. In addition, the frequent hospital admission and prolonged hospital stays significantly impact these patients' quality of life and places them at risk of acquiring further nosocomial infections [29].