Original

Immunizable diseases and Down syndrome

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Abstract

People with Down syndrome (DS) are especially infection-prone, particularly during childhood. The main reason is an association of DS with multifactorial primary immune deficiency. Many of these conditions are immunizable, but studies of vaccination and DS are few and do not include recent formulations. While awaiting remediation of this gap, the present state of knowledge is that available vaccines are safe and effective for people with DS, though the possibility that response may be lower than average means that strict compliance with immunization schedules is required to ensure effectiveness.

Keywords: Down syndrome. Active immunization. Vaccination. Passive immunization.

Introduction

Down syndrome (DS) is associated with a primary immune deficiency that leads to a particularly high prevalence of infectious and autoimmune disease (1). While this immune deficiency is multifactorial, its ultimate causes and the role played by different immune functions are yet to be identified (2, 3). There has been some discussion of the possibility that preventive immunization might therefore induce a diminished response in people with Down syndrome, but little research has been carried out in this area –except for hepatitis B– and study findings are contradictory. Generally speaking, despite some less-than-clear response patterns to antigens in vaccines, it is fair to conclude that indications, administration, and safety profiles for people with DS are comparable to those determined for the general population. However, the specific nature of this syndrome justifies a general reminder of the impact of some diseases that can be prevented by vaccinating carriers, and an update on immunization recommendations.

Hepatitis B

Over the last third of the 20th century, a considerable number of Spanish and other studies and papers in Spain and abroad sounded the alarm and warned of high prevalence rates of hepatitis B virus (HBV) infection among people with mental disabilities, especially those with Down syndrome. They also showed that a large percentage of infected individuals were chronic carriers (HBsAg + / HBeAg +) (4-9). Most patients were inmates of institutions. Serum testing studies documented prevalence rates ranging from 30 to 90%, with the percentage of chronic carriers rated as potentially higher than 20 or even 30% (5, 7, 10, 11). These rates were significantly higher than those recorded for other inmates (up to 25% seropositive, and about 4% chronic carriers), which were in turn far higher than the rates for the general population (lessfewer than 2% were chronic carriers in Spain) (5). These findings were quite striking and HBV became the

best-studied immunopreventable disease in DS; as a result, its biological and epidemiological conditioning factors were assessed and preventive measures were adopted.

Several factors may be involved, and possibly converge, in the presumed vulnerability of people with DS to HBV:

a) A defective immune response to viral infection. This may start with a low specific humoral response to HBsAg (1, 2), in particular, inadequate protective action from some IgG subclasses, notably IgG1 (12). Afterwards, defective cell-mediated immunity malfunctioning T-cells and NK-cells, specifically may impede the elimination of the infecting virus, turning many patients into chronic carriers (2, 10).

b) Persistent exposure to chronic carriers or acutely infected patients. Extended contact among inmates or boarders at closed institutions for people with intellectual disabilities was classically viewed as the chief means of transmission of HBV, with risk of acquistion directly proportional to the size of the center and duration of stay, and inversely proportional to age of institutionalization (4, 5, 10). Still, some studies have found similar prevalence rates for people attending non-boarding institutions (8, 10), whereas children with DS who live at home in early childhood and attend mainstream schools or early intervention centers have infection rates below 5%, similar to those for all other children with the same kind of schooling (8, 11, 13). This means that DS as such plays a very secondary role in HBV pathogenesis. Risk of acquisition is heightened when the child starts school (7), but this risk is shared, though at a smaller scale, by all other children.

c) Behavioral and somatic characteristics of DS. These characteristics may contribute to the spread of the disease, even if only accessorily. A protruding tongue and a love of public displays of affection are Some of among the traits that have been highlighted in this regard are public displays of affection and tongue protrusion, especially in children and teenagers; both would appear to foster horizontal spread via saliva secretions of infected persons (5, 7, 14).

Repercussions of HBV infection and Down syndrome

The more serious complications of hepatitis B, chiefly, cirrhosis and liver cell carcinoma, develop late and affect the infection's target organ. Nothing specifically pertaining to DS can be found in the literature, perhaps because the low life expectancy ofin the past did not enable a comparison with the general population rates.

An especially active viral replication phase and a high rate of chronic carriers among infected patients with Down syndrome are two factors that propitiate and prolong transmission of the virus and hence contagion of schoolmates, caregivers or teachers (4, 5, 8, 9). This was substantiated in the United States in 1975, when legislation stipulated admission into public mainstream day schools of people with mental disabilities who had been institutionalized up until then (4).

Hepatitis B vaccination and Down syndrome

The tapering off of institutionalized care, boarding facilities, and separate special education schools for people with DS has played a key role in limiting hepatitis B risk in this group. Some factors remain, such as disease proneness, specific developmental patterns, and the subsisting need for special schools or sheltered workshops for some. The ensuing risk to the individual and the community can only be addressed by active immunization.

Despite the defective immune response discussed above, on the whole the effectiveness of hepatitis B vaccination of people with DS is satisfactory. Seroconversion rates range from 73 to over 90%, practically matching the rates for the mainstream population (6, 15-17). Age correlates inversely with the rate of induced protective antibodies, as for the non-DS population but in a more pronounced manner. There are significantly more respondents among subjects younger than 30 or 40 years, especially those under 14 (10, 15, 16), and the response rate is in fact 100% among preschool children (18, 19), whereas up to 25% of institutionalized adults may be non-responders (9). Specific below-average IgG subclass responses have been found among adults with DS (20), plausibly reducing the efficacy of vaccination. Vaccination always induces protective geometric mean titres (GMTs) of anti-HBs antibodies in people with DS, which remain protective even though their rate of decline is slightly faster than usual (9, 16-19). As for other patients, incorrect administration such as injection in the buttocks or obesity a frequent condition

among people with DS may cause immunization to fail (6, 15). In these cases, as in any others in which effective immunization must be ensured, post-vaccination serological testing for protective titres (10 IU/L or higher) is advisable.

Hepatitis B and Down syndrome: conclusions

From the present state of knowledge we may infer the following conclusions:

a) The population with DS is particularly vulnerable to HBV infection, which may acquire evolutionary traits that make the condition more likely to become chronic and more infectious. Because of this, all possible preventive measures must be adopted to protect the individuals themselves and other people who interact with them at close quarters.

b) Mainstream schooling and employment of people with DS have significantly reduced the ease of transmission of HBV among this group.

c) Because of b) and of their well-substantiated good immune response to hepatitis B vaccination, and bearing in mind current universal vaccination strategies, it is fair to state that people with DS do not constitute a special group where HBV vaccination is concerned (15, 19); they should be immunized using community-standard dosage regimens and administration forms. Generally speaking, vaccination should take place within months of birth, with revaccination only to be considered in the presence of highly specific treatments or conditions not including DS.

d) Whenever vaccination has not been carried out during infancy as recommended above, the vaccine should be administered as early as possible, preferably before the child begins school, in order to maximize immune response, prevent transmission risks, and forestall the appearance of factors that might reduce immunogenicity, such as overweight or ageing (6, 7, 10, 21).

e) If an individual is to attend institutions for people with learning disabilities, whether as an inmate, boarder or day student, full immune status must be verified and ensured. Staff at these institutions should also be immunized, as there are good chances that they will enter into contact with acutely or chronically infected patients.

Hepatitis A

Since the chief transmission mechanisms of hepatitis A are person-to-person physical contact and contaminated food or drink, its high prevalence rate among institutionalized people with mental disabilities makes perfect sense, as in the case of hepatitis B. Despite the near-disappearance of institutionalization by now, several factors remain that make hepatitis A vaccination advisable for individuals with DS: namely, their potential susceptibility given their deficient immune systems; the need for frequent attendance at specialized centres that might contribute to the spread of the infection; and their proneness to chronic hepatitis B infection, which can make co-infection with hepatitis A particularly serious (22). Hence, these individuals should always be vaccinated against hepatitis A, either in the context of the general routine immunization schedule or as a specific high-risk group. In Spain, only Ceuta and Melilla include this vaccine across the board for all children during their second year of life. In Catalonia, universal vaccination is carried out in the teenage years. These differing strategies are based on different epidemiological profiles.

The hepatitis A vaccine may be administered after the child turns one. The monovalent form consists of two injections within 6 to 12 months of each other. This schedule has been shown to be safe and effective in children with Down syndrome, who achieve seroconversion rates of 100% (23). The combined hepatitis A and B formulation is administered in 3 doses at 0, 1 and 6 months from the date of first injection.

Pneumococcal disease

Pneumococcal infections have one of the highest morbidity and mortality rates worldwide, particularly among children under 5 years and elderly persons. All Spanish communities include pneumococcal polysaccharide vaccination in their routine schedules for persons over 60 or 65 years, independent of any other risk factor.

In pediatric practice, *Streptococcus pneumoniae*, or pneumococcus, is the chief etiological agent of acute otitis media (AOM); the main cause of acute respiratory infections; and the second most common cause of invasive diseases and meningitis in Spain, after meningococcus. The predisposition of children with DS to ear and airway infections is well documented, often with severe or recurrent manifestations and giving rise to no few short- and long-term complications such

as pleural pneumonia or hearing loss. The high risk of septic death in these children has also been highlighted, with pneumococcus among the main causal agents (24). National studies under way are looking at DS as a potential risk factor for invasive pneumococcal disease. This substantiates the interest of having children with DS under 5 years receive the conjugate heptavalent pneumococcal vaccine (VNC-7v), which is not included in official schedules adopted by Spain's national health system. Among the general pediatric population, this vaccine is more than 95% effective at preventing meningitis and systemic infections, highly effective at preventing bacteremic pneumonia, and significant for AOM.

A search of medical literature currently turns up only two studies of antipneumococcal vaccination of people with DS (25, 26). Both trials investigated the same non-conjugate polysaccharide vaccine in adults and children over 5 years, and both showed a significant increase in anti-*S. pneumoniae* serum antibodies compared to prevaccination levels, which were much lower against all vaccine serotypes in children with DS than in the child control group. Although induced levels in the study groups were on the whole slightly lower than in the control groups in both trials, they remained withn ranges that confer a protective effect. These findings support the need to indicate VNC-7v for children with DS younger than 60 months, either as a high-risk group, as is currently the case in Catalonia and other autonomous communities of Spain, or as part of the general official routine schedule, as is the case in Madrid at present. Further study of the immunogenic response of children with DS to conjugate vaccines is required, including consideration of soon-to-be-marketed new-generation vaccines with a higher antigen payload.

Haemophilus influenzae type b (Hib) and meningococcal serogroup C (MenC) infection

In Spain, mass administration of Hib vaccines to children under 5 (since 1994) and of MenC vaccines to children and adolescents (from 2001-2002) has practically eradicated these types of infection through direct and indirect effects. Only a few sporadic cases are to be expected now, either among pockets of susceptible children - – usually among marginal populations - – or due to vaccine failure, - an unusual occurrence. It must be remembered that Hib vaccination failure may be caused by deficient levels of IgG2, which provides protection against encapsulated microorganisms. Abnormally low levels are thought to occur at a higher-than-usual rate among children with DS.

Influenza

In the childhood years, DS-related infection-proneness tends to manifest particularly in the respiratory tract. During the first 5 years of life, particularly the first, morbidity and mortality rates are far higher than rates for the general population. The influenza virus is among the most frequent causes of respiratory conditions in these cases, and induces a significant number of bacterial complications such as acute otitis media or pneumonia. Anomalous immune responses to influenza viruses have been documented in people with DS (27).

The few existing studies of inactivated flu vaccine immunogenicity among people with DS have divergent findings. Whereas some researchers have documented deficient in vitro T-cell proliferative response and humoral response (27), others have found that humoral response to vaccination was not significantly different from control-group levels for the majority of circulating influenza antigens (28, 29).

Annual flu vaccination is indicated for high-risk groups: elderly persons, social workers, and patients with certain types of chronic conditions (whether cardiovascular, bronchopulmonary, renal, or metabolic) (22). These diseases are not unusual among people with DS. Present knowledge supports the inclusion of people with DS as a specific high-risk group, independent of any other predisposing factors. This is particularly advisable for children with DS aged 6 months to 5 years, who already receive routine immunization in several Western countries.

Diphtheria, tetanus and whooping cough (pertussis)

Humoral responses to diphtheria and tetanus toxoids in subjects with DS have been shown to be equivalent to those for non-DS subjects (29, 30), although deficient in vitro T-cell and IgG responses to the tetanus antigen have been documented (27). Acellular pertussis vaccines induce adequate levels of protective antibodies in children with DS, even though IgG GMTs for *B.*

pertussis have been found to be lower than GMTs in controls (31).

«Childhood diseases» measles, mumps, rubella, chickenpox, and polio

While these are not exclusively diseases of childhood, they were classified as such in the past because of their high predilection for the childhood years. There are no studies of recently developed vaccines (such as chicken pox or enhanced-potency inactivated polio vaccine) and DS. Studies of other vaccines in this subsection are now outdated, and were mostly carried out in institutions for the disabled, in which epidemiological conditions are a far cry from current typical living arrangements. The seroconversion rates in those studies are similar to control-group rates for measles, mumps, and rubella, though humoral response is lower for measles and rubella (32). Oral polio vaccine induced antibody titers similar to those for the general population for types 2 and 3, but lower titers for type 1 (32).

Other immunizable diseases

Rotaviruses are the most common cause of gastroenteritis in children under 5 years and induce the most serious cases. Although no specific research has been carried out, infants with DS should benefit from rotavirus vaccination; their poor immune status is not an indication unless it is concurrent with uncorrected gastrointestinal (GI) tract malformations. Acute and recurring bouts of gastroenteritis are second highest cause of infectious disease in DS, behind respiratory diseases.

Human papillomavirus (HPV) infection is a necessary prerequisite to the development of cervical cancer. With the recent introduction of HPV vaccination in the routine immunization schedule for girls aged 11 to 14 years, teenage girls with DS will be protected.

Respiratory syncytial virus (RSV)

The most serious forms of RSV-induced bronchiolitis develop in babies with certain risk factors, such as age under 3 months, congenital heart disease, chronic lung disease, or preterm birth at a gestational age of less than 34 weeks. DS has currently been proposed for inclusion in this list of independent risk factors; hence, newborns and babies with DS should be directly considered for passive monoclonal antibody prophylaxis (palivizumab) (33). In the future, RSV vaccination will enable more cost-effective prevention strategies than those currently available.

Conclusions

There are few studies of vaccine immunogenicity in people with DS, and almost none exist for the latest formulations. Available data suggest satisfactory rates of immune response to vaccination in this population, though in some cases they are significantly lower than usual. These facts, coupled with some of the features of DS itself, lead to a number of considerations regarding immunization of people with DS.

Further studies are needed.

People with DS should be included in the routine immunization schedules for the general population, while keeping in mind the need for some specifically indicated vaccines because of the immune traits and even some of the morphological features of DS.

Vaccines must be administered correctly at the correct dosage; strict compliance in this regard is essential to ensure immunogenicity.

Health care programs for people with DS should include post-vaccination serum testing, in case revaccination or booster doses are called for.

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