Live Vaccine in Children with DiGeorge/22q11.2 Deletion Syndrome

Vacinas Vivas em Crianças com Síndrome de DiGeorge/ Deleção 22q11.2

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ABSTRACT

Introduction: Children with DiGeorge syndrome/chromosome 22q11.2 deletion syndrome might have a variable degree of immunodeficiency, which may limit the use of live vaccines. The aim of this study was to review the adverse effects of live vaccines and possible relation with immune status in patients with DiGeorge Syndrome/partial 22q11.2 deletion syndrome.

Material and Methods: Retrospective study with analysis of the clinical records of children with chromosome 22q11.2 deletion syndrome and DiGeorge syndrome phenotype, followed in a Primary Immunodeficiency center. Data were collected on: demographic characteristics; medical and vaccination history with live vaccines; T-CD4+ lymphocyte counts and lymphocyte proliferative responses to antigens and mitogens; adverse reactions; vaccine failure.

Results: Twenty three children with DiGeorge syndrome/22q11.2 deletion syndrome were included, 65.2% male, with average age at diagnosis of 11.3 months. Eighteen children (78%) received bacillus Calmette-Guérin vaccine: all with evidence of thymic activity; three presented moderate T-CD4+ lymphopenia and abnormal lymphocyte proliferative responses; one had abnormal lymphocyte proliferative responses for mitogens, four for purified protein derivative and one for tetanus toxoid. Measles, mumps and rubella vaccine was administered to 15 children, three of them with moderate immunosuppression and abnormal lymphocyte proliferative responses. Live attenuated polio vaccine was administered to 4 children without immunosuppression and the rotavirus vaccine to three children, one with moderate immunosuppression. No significant adverse reactions were reported.

Discussion: These data are in line with the findings of other international studies.

Conclusion: In our sample, live vaccines were well-tolerated, even in children with moderate T-CD4+ lymphopenia and abnormal lymphocyte proliferative responses to antigens/mitogens.

Keywords: Child; Chromosome Deletion; Chromosome Disorders; Chromosomes, Human, Pair 22; DiGeorge Syndrome; Vaccines, Attenuated/adverse effects; Viral Vaccines/adverse effects

RESUMO

Introdução: A síndrome de DiGeorge/deleção 22q11.2 pode apresentar um grau variável de imunodeficiência, condicionando a utilização de vacinas vivas. Este estudo teve como objetivo documentar os efeitos adversos de vacinas vivas e possível relação com alterações imunitárias em crianças com síndrome de DiGeorge/deleção 22q11.2 parcial.

Material e Métodos: Foi realizado um estudo retrospetivo por revisão dos processos clínicos das crianças com deleção do cromossoma 22q11.2 e fenótipo de síndrome de DiGeorge, seguidos num centro de referência de imunodeficiências primárias. Foi realizada colheita de dados, incluindo: características demográficas; história médica; historial de vacinação com vacinas vivas; contagem de linfócitos T-CD4+ e respostas proliferativas linfocitárias a antigénios e mitogénios; reações adversas; falências vacinais.

Resultados: Foram incluídas 23 crianças com síndrome de DiGeorge/deleção 22q11.2, 65,2% do sexo masculino e idade média de diagnóstico de 11,3 meses. Destas, 18 crianças (78%) receberam a vacina *bacillus* Calmette-Guérin: todas com evidência de atividade tímica; três apresentaram linfopénia T-CD4+ moderada e respostas proliferativas linfocitárias anormais; uma com respostas proliferativas linfocitárias anormais para mitogénios, quatro para derivado de proteína purificada e uma para toxóide tetânico. A vacina tríplice contra o sarampo, parotidite e rubéola foi administrada a 15 crianças, três com imunossupressão moderada e respostas proliferativas linfocitárias anormais. A vacina viva atenuada contra poliomielite foi administrada a quatro crianças sem imunossupressão e a vacina contra o rotavírus a três crianças, uma com imunossupressão moderada. Não foram reportadas reações adversas.

Discussão: Estes dados estão de acordo com as conclusões de outros estudos internacionais.

Conclusão: Na nossa amostra, as vacinas vivas atenuadas foram bem toleradas, incluindo em crianças com linfopénia T-CD4+ moderada e com respostas proliferativas linfocitárias a antigénios/mitogénios anormais.

Palavras-chave: Criança; Cromossomas Humanos Par 22; Deleção Cromossómica; Síndrome de DiGeorge; Transtornos Cromossómicos; Vacinas Atenuadas/efeitos adversos; Vacinas Virais/efeitos adversos

INTRODUCTION

DiGeorge syndrome (DGS) is usually associated with chromosome 22q11.2 microdeletion, mostly due to de novo mutations or corresponding to autosomal dominant transmission. It is one of the leading chromosomal disorders,

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with a frequency of 1 from each 3,000 to 6,000 deliveries.[1–3] Chromosome 22q11.2 deletion (22q11.2DS) can also be found in other syndromes including the velocardiofacial syndrome.[2–4]

Conotrunchal heart defects, thymic hypoplasia and hypocalcaemia (due to parathyroid hypoplasia) correspond to the classic triad of features of DGS on presentation. However, the phenotype is highly variable and could be associated with immune defects and anatomic abnormalities, among others.[2,5]

Around 75% of the patients with 22q11.2DS present with mild to moderate immunodeficiency due to thymic hypoplasia and impaired T-cell production or mildly impaired T-cell function, with variable clinical expression (partial DGS). The age-related rate of decline of T-cell numbers is slower in patients with T-cell lymphopenia than controls, due to the expanded pool of memory T-cells.[6–8] Complete DGS is presented by less than 1% of cases, corresponding to a type of severe combined immunodeficiency.[1,5–7]

Humoral immune deficiency associated with partial DGS is mainly related to IgA deficiency and poor response to polysaccharide antigens.[7,9]

The use of live vaccines is contraindicated in patients with severe T-cell immunodeficiency, even though it could be considered in children with mild or moderate T-cell immunodeficiency, such as in children with partial DGS. Avoidance of live vaccines has been questioned as the risk of natural infection remains unchanged and there is an increasing evidence of normal T-cell function in most children with DGS.[10–12]

Some authors have suggested that live vaccines could be safely administered in children older than one year of age diagnosed with DGS, presenting with the following criteria: presence of antibodies for inactivated vaccines; normal or near normal proliferative responses to antigens and mitogens; CD8+ T-cell count >300 cells/mm^3; CD4+ T-cell count >500 cells/mm^3.[10,13]

Regular measurement of the levels of antibodies (each 6 to 12 months) and re-immunisation could be necessary in children with DGS as sustaining protective antibody levels could be lower than in age-matched control subjects.[13]

Few studies have characterised the use and adverse events associated with live vaccines in children with DGS. This study was aimed at contributing to the assessment of safety of live vaccines regardless of whether or not these were introduced into the National Program of Vaccination [*Programa Nacional de Vacinação* (PNV)] and describing any relationship between the presence of immune system disorders and the risk of complications in children with partial DGS.

MATERIAL AND METHODS

This was a retrospective study of children with 22q11.2DS [confirmed by fluorescence in situ hybridization (FISH)] and the DGS phenotype having attended the outpatient clinic of primary immunodeficiency disorders at the *Centro Hospitalar de Lisboa Norte* from 2000 to 2016. The following data were collected from the clinical records: demographic characteristics (gender and age); age at diagnosis; clinical complications (including cardiac, respiratory, ENT (ear, nose and throat) or endocrine pathology, absent thymus); history of vaccination with live attenuated vaccines and date of administration, including Bacillus Calmette-Guérin (BCG) vaccine, MMR (measles, mumps and rubella) vaccine, oral live-attenuated polio vaccine (OPV) and rotavirus vaccine (Rotateq® or Rotarix®); local adverse reactions occurring up to 12 months following BCG vaccine or 56 days following the remaining live vaccines; history or medical record of vaccine-preventable disease; blood lymphocyte immunophenotyping (by flow cytometry) and proliferative responses to antigens and mitogens. In the absence of any medical record, data were obtained by postal or telephone questionnaire sent to parents / legal caregivers.

The presence of clinical signs or symptoms suggesting an adverse reaction to a previously administered vaccine, according to physicians that have examined the patients and have recorded the information either on patient's *Boletim de Saúde Infantil e Juvenil* (Child and Youth Health Book) or in a specific report was defined as adverse events associated with live vaccines. Any information on the presence of local abscesses, lymphadenitis, bone infection, multifocal skin lesions and disseminated disease (lymph node, pulmonary, liver / splenic, ocular or meningeal involvement) related to BCG was surveyed. Hospital admissions, morbidity and mortality related to any adverse event were surveyed as well.

Vaccine-preventable diseases including measles, mumps, rubella and rotavirus, affecting children having completed the vaccination schedule were considered. Diagnosis was based on patient's clinical history, examination and/or laboratory confirmation (required in the case of rotavirus infection).

Our group of patients was characterised as presenting with (i) severe immunosuppression when < 15%, (ii) moderate, 15% - 24% and with no evidence of immunosuppression when ≥ 25%, according to CD4 percentage.

The percentage of recent thymic emigrants was classified as normal if adequate, or abnormal if reduced or absent. Proliferative responses to specific antigens and mitogens were classified as normal if positive or adequate and abnormal if reduced or absent. Lymphocyte proliferation assays were carried out at the laboratory of clinical immunology of the *Instituto de Medicina Molecular* (Faculty of Medicine of the University of Lisbon).

A descriptive analysis of the demographic characteristics, clinical history, immune function, history of vaccine-preventable diseases in immunised patients, adverse events and vaccination coverage.

Caregivers of eligible patients were informed and their informed consent was obtained for the participation in the study. The regulations established by the Clinical Research and Ethics Committee of the institution have been followed and their approval has been obtained.

RESULTS

Study sample

A total of 23 patients born between 1999 and 2015 diagnosed with DGS and with postnatal confirmation of chromosome 22q11.2 deletion by FISH or array CGH technique were included in the study. Genetic confirmation was mostly obtained within patient's first year of life (Table 1). Several patients were vaccinated before the diagnosis of 22q11.2DS / DGS was reached.

Six patients with thymic aplasia were found, most patients presented with haemodynamically significant cardiac disease (n = 15/65.2%) and underwent cardiac surgery (n = 10/43.5%). An early confirmation by FISH was obtained for most patients with cardiac disease and were rarely exposed to live vaccines within their first year of life.

Four out of 21 patients with a confirmed diagnosis (two unknown results) presented with moderate immunosuppression (19%) and two of these presented with immunosuppression within their first year of life. Severe immunosuppression was not presented by any patient in our group.

Three patients with reduced thymus activity were found. Most patients presented with normal responses to mitogens. However, half of the patients presented with abnormal proliferative responses to specific antigens (n = 12/52.2%). Abnormal proliferative responses to tetanus toxoid were found in four patients, three of these showing abnormal proliferative responses to the purified protein derivative (PPD) and one patient showing moderate immunosuppression

Table 1 – Characteristics of our group of patients

Total	23
Demographic	
Male gender, % (n)	65.2% (15)
Clinical history	
22q11.2 deletion, % (n)	
Posnatal testing	100.0% (23)
Age at confirmation of diagnosis, (months)	
Mean	11.3
Range	1 – 74
Thymic aplasia, % (n) (total = 8) [a]	26.1% (6)
Exploratory surgery	13.0% (3)
Cardiac disease, % (n)	65.2% (15)
Cardiac surgery, % (n)	43.5% (10)
Mortality, % (n)	4.3% (1)
Immune system	
CD4+, % (n) (total n = 21) [b]	
No evidence of immunosuppression (≥ 25%)	80.9% (17)
Moderate immunosuppression (15% - 24%)	19.0% (4)
Severe immunosuppression (< 15%)	0
CD31, CD45RA, % (n) (total n = 21) [b]	
Reduced	14.3% (3)
Normal	85.7% (18)
Proliferative responses to mitogens, % (n) (total n = 16) [b]	
Reduced	6.25% (1)
Inconclusive results	6.25% (1)
Normal	87.5% (14)
Proliferative responses to antigens[b]	
Purified protein derivative (PPD), % (n) (total n = 16)	
Reduced / absent	25.0% (4) / 25.0% (4)
Normal	50.0% (8)
***Candida albicans* (CA), % (n) (total n = 15)**	
Reduced / absent	40.0% (6) / 33.3% (5)
Normal	26.7% (4)
Tetanus toxoid (TT), % (n) (total n = 10)	
Reduced / absent	20.0% (2) / 20.0% (2)
Normal	60.0% (6)

[a] Data on the presence of thymus were only available in eight patients; [b] CT-cell count, pre-immunisation data on proliferative responses to antigens and mitogens were unavailable for all patients.

(CD4+ rate of 22.9%/1,056 cells/μL); all the patients had received the entire tetanus immunisation schedule for the age (one patient had completed the schedule less than one month before the study).

One patient (presenting with normal immunity) died prematurely due to cardiac comorbidities.

Vaccine-preventable diseases

None of the patients presented with any laboratorial, clinical or diagnostic confirmation of any of the vaccine-preventable diseases related to the live vaccines included in the study (including patients who underwent the entire immunisation schedule against that disease).

Vaccination coverage and adverse events associated with live vaccines

The detailed results of each vaccine are shown in Tables 2 and 3.

BCG vaccine was administered to 19 (82.6%) patients: 17 with an evidence of thymic activity, based on the presence of *naïve* T-cells recently migrated from the thymus (CD31+). Three patients out of these presented with moderate immunosuppression, with CD4+ lymphopenia (15-24%) and abnormal proliferative responses. Five out of the 14 patients with normal CD4+ counts showed abnormal proliferative responses, while inconclusive results were obtained in one patient.

MMR vaccine was administered to 15 (65.2%) patients: the evidence of thymic activity was shown by all the 14 patients with known testing results. Three patients presented with moderate immunosuppression with CD4+ lymphopenia and abnormal proliferative responses; four out of the 11 patients with normal CD4+ counts presented with abnormal proliferative responses.

OPV vaccine was administered to four (17.4%) patients, all showing an evidence of thymic activity. All patients presented with normal CD4+ counts, one with inconclusive results regarding proliferative responses to mitogens and three patients showing abnormal results. The presence of no patient having received the OVP vaccine with immunosuppression probably reflects an intentional avoidance of the vaccine in children with T-cell impairment.

Rotavirus vaccine was only administered to two patients (one with a complete schedule of Rotateq® and one with Rotarix®): an evidence of thymic activity has been found in both. One patient presented with moderate immunosuppression with CD4+ T-cell lymphopenia, showing normal proliferative responses to mitogens.

No adverse event was described for any vaccine within the post-vaccination period defined for each vaccine. No hospital admissions or mortality was associated with any of the live vaccines that were included in the study.

DISCUSSION

In our group of patients, no significant adverse events associated with live-attenuated vaccines were found in patients with 22q11.2DS / DGS, including patients with moderate CD4+ T-cell lymphopenia and with reduced proliferative response to mitogens and antigens. No patients presented with severe immunosuppression, which is a formal contraindication for the administration of live vaccines.[1,5–7]

These data are in line with the conclusions of other recent studies: (i) in one retrospective study of 82 patients with DGS, only six patients (7.3%) showed mild adverse events associated to the use of MMR vaccine (similar incidence to the general population), with no moderate or severe adverse events; (ii) in a multi-centric retrospective study with 194 patients with DGS, with a 77% MMR vaccine coverage, including 35 patients with moderate immunosuppression and six with severe, only 14% of the patients showed adverse events following MMR vaccine, mostly mild events, with no associated mortality. Both studies have reached the conclusion that live vaccines were frequently administered to patients with DGS and were generally well-tolerated in patients with mild to moderate immunosuppression.[1,13]

Some limitations of this study are worth mentioning, particularly related to the small size of our group of patients and to its retrospective design, with data collected from patient's caregivers when no clinical records existed, reducing its objectivity. Even though this was a descriptive study, it has the merit of having been adapted to the national immunisation schedules, including vaccines listed in the PNV and out of the national program, with no specific monitoring.

Controlled, randomised, prospective studies involving representative samples are needed to establish formal recommendations for the use of live vaccines in patients with

Table 2 – Vaccine coverage, adverse events and vaccine-preventable diseases

Immune system disorders (Total, n)	BCG	MMR	OVP	Rotavírus	Adverse events associated to vaccines	Vaccine-preventable diseases
No evidence of immunosuppression (17)	16	12	4	1	No	No
Moderate immunosuppression (4)	3	3	—	1	No	No
Reduced thymus activity ↓ (3)	2	2	1	—	No	No
Reduced PR to mitogens ↓ (1)	1	1	—	—	No	No
Reduced ↓ /absent PR to antigens						
PPD (8)	7	6	2	1	No	No
CA (11)	8	7	2	2		
TT (4)	3	2	1	1		

BCG: Bacillus Calmette-Guérin vaccine; MMR: measles, mumps and rubella vaccine; OVP: oral live-attenuated polio vaccine; PR: proliferative responses; PPD: purified protein derivative; CA: *Candida albicans*; TT: tetanus toxoid

Table 3 – Immunological characteristics and morbidity/mortality of vaccine-preventable diseases

Live vaccine	BCG	MMR	OVP	Rotavírus
Total, % (n) (total n = 23)	82.6% (19)	65.2% (15)	17.4% (4)	8.7% (2)
Immune system				
CD4+, % (n)				
No evidence of immunosuppression (≥ 25%)	73.7% (14)	73.3% (11)	100.0% (4)	50.0% (1)
Moderate immunosuppression (15% - 24%)	15.8% (3)	20.0% (3)	0	50.0% (1)
Severe immunosuppression (< 15%)	0	0	0	0
Unknown	10.5% (2)	6.7% (1)	0	0
CD31, CD45RA, % (n) [a]				
Reduced	10.5% (2)	13.3% (2)	25.0% (1)	0
Normal	89.5% (17)	80.0% (12)	75.0% (3)	100.0% (2)
Proliferative responses to mitogens % (n) [a]				
Reduced	5.3% (1)	6.7% (1)	0	0
Normal	52.6% (10)	60.0% (9)	25.0% (1)	100.0% (2)
Inconclusive results / not carried out	42.1% (8)	33.3% (5)	75.0% (3)	0
Proliferative responses to antigens[a]				
Purified protein derivative (PPD), n				
Reduced / absent	36.8% (7)	40.0% (6)	50.0% (2)	50.0% (1)
Normal	26.4% (5)	26.7% (4)	50.0% (2)	50.0% (1)
Inconclusive results / not carried out	36.8% (7)	33.3% (5)	0	0
***Candida albicans* (CA), n**				
Reduced / absent	42.1% (8)	46.7% (7)	50.0% (2)	100.0% (2)
Normal	15.8% (3)	20.0% (3)	50.0% (2)	0
Inconclusive results / not carried out	42.1% (8)	33.3% (5)	0	0
Tetanus toxoid (TT), n				
Reduced / absent	15.8% (3)	13.3% (2)	25.0% (1)	50.0% (1)
Normal	26.3% (5)	33.3% (5)	50.0% (2)	50.0% (1)
Inconclusive results / not carried out	57.9% (11)	53.4% (8)	25.0% (1)	0
Adverse events associated with vaccines, n[b]		0		
Vaccine-preventable diseases, n[c]		0		
Mortality associated with vaccines, n		0		

[a] T-cell count, pre-immunisation proliferative responses to antigens and mitogens were not available for all patients; [b] Considering a 12-month window period for BCG and 56 days for other live vaccines; [c] Vaccine-preventable diseases in patients who have completed the entire immunisation schedule (measles, mumps, rubella, rotavirus).
BCG: Bacillus Calmette-Guérin vaccine; MMR: measles, mumps and rubella vaccine; OVP: oral live-attenuated polio vaccine.

22q11.2DS / DGS (including, for instance, the definition of a minimum level of CD4+ T cell count from which the use of live vaccines would be safe). Until then, the decision whether to use live vaccines should be individualised.[1,5,13]

CONCLUSION

In our group of patients, the use of live-attenuated vaccines was well-tolerated, including in patients with mild to moderate immunosuppression. This study was aimed at giving a contribution to a meta-analysis of similar studies, leading to recommendations on the use of live vaccines in patients with 22q11.2 microdeletion syndrome / DiGeorge syndrome.

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HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data. Informed consents were obtained.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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