

Isolated loss of vaccine immunity in the protein losings syndrome in a patient with a reverse one and a half ventricle palliation (“failing Fontan-like physiology”)

Original Article

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Abstract

Background: A subgroup of CHDs can only be treated palliatively through a Fontan circulation. In case of a failing Fontan situation, serum proteins are lost unspecifically and can also lead to a loss of vaccine antibodies. In a failing Fontan situation, heart transplantation may be the only feasible option. **Patient:** We describe a 17-year-old patient born with a hypoplastic left heart complex, who underwent Fontan completion at the age of 4 years and developed a failing Fontan physiology. Therefore, a Fontan takedown with creation of a reverse 1½-circulation was performed. Multiple exacerbations of protein losing enteropathy occurred with a hypoproteinaemia, hypalbuminaemia, and hypogammaglobulinaemia. The patient was hospitalised several times and treated with intravenous application of immunoglobulins and albumin for symptom control. Before one of this substitutions, the immunoglobulin G against measles, mumps, and rubella was determined: the patient’s serum demonstrated a positive measles and rubella, but mumps was negative. After administration of the iv-therapy, the lacking antibodies were replenished, and there was a positive test for mumps. **Method:** Serum samples were analysed by neutralisation test and enzyme-linked immunosorbent assay (ELISA). **Conclusion:** Although the patient had been vaccinated according to national guidelines, we saw an intermittent immune deficiency for mumps, but not for rubella and measles. For patient with a failing Fontan circulation, we recommend to test to vaccine antibodies for mumps, measles, and rubella with an ELISA an if its negative with a neutralisation test, especially in view of a possible heart transplantation to find a possible immune deficiency.

Introduction

A subgroup of congenital heart defects (CHD) can only be treated palliatively, especially for patients with a univentricular circulation. Since Fontan described the procedure in 1968, a multitude of variations have been adopted that all lack a subpulmonary ventricle and establish direct drainage of systemic venous return to the lungs.^{1–4} In a failing Fontan situation, serum proteins are lost nonspecifically into the gut and are often replaced by intravenous immunoglobulin or albumin to maintain the oncotic blood pressure. This is often done to palliate symptoms such as ascites, diarrhoea, or generalised lymphedema.^{1–6} Loss of serum proteins may also lead to loss of vaccine-induced antibodies. Especially for patients with a failing Fontan, heart transplantation might be the only feasible option.^{1,7,8} Since vaccination with live-attenuated vaccines is contraindicated in transplanted and immunosuppressed patients, exploring the immune status and closing vaccination gaps in case of insufficient protection prior to transplantation is mandatory for this group of patients.⁹ The German Standing Commission on Vaccination at the Robert Koch Institute publishes yearly recommendations. Besides the routine immunisation schedule, the German Standing Commission on Vaccination also recommends vaccinations for specific indications or target groups. For measles, mumps, and rubella, a two-dose schedule with the measles, mumps, and rubella combination vaccine is recommended by the German Standing Commission on Vaccination to be administered routinely at the age of 11 and 15 months.¹⁰ Those ≥18 years and born after 1970 with unclear vaccination status, who have not been vaccinated, or who received only one vaccination during childhood should receive one dose of measles, mumps, and rubella.¹¹

For routine cases, it is recommended to check the vaccination status using the vaccination certificate. Determination of the vaccination titres might be required when the documents are missing or due to a certain clinical condition. This case report describes a patient in a failing Fontan-like situation with protein-losing enteropathy.

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Case report

We describe a 17-year-old patient born with a hypoplastic left heart complex (HLHS) (Shone complex type of borderline HLHS including endocardial fibroelastosis). Our patient underwent Fontan completion at the age of 4 years using a fenestrated 19 mm extracardiac total cavopulmonary connection conduit. During follow-up, he developed a failing Fontan physiology due to increasing pressure values in the Fontan circuit. Therefore a Fontan take-down with the creation of a reverse 1½-circulation was performed (hemi-Mustard plus Glenn resulting in an inferior vena cava via mitral valve, left ventricle to pulmonary circulation, and a subsystemic right ventricle).^{12–14}

Nevertheless, multiple exacerbations of protein-losing enteropathy with formation of ascites and diarrhoea occurred. Currently, the patient has limited exercise capacity (New York Heart Association Class III–IV), is unable to attend school, is susceptible to infection, and suffers from chronic mucopurulent cough and osteoporosis. Laboratory results show the failing Fontan-like physiology in permanent hypoproteinaemia < 50 g/l (normal value 65–82 g/l) hypalbuminaemia (< 28 g/l (normal value 32–48 g/l), and hypogammaglobulinaemia (IgA < 0.2 g/l (normal value 0.7–4), immunoglobulin G (IgG) < 3 g/l (normal value 8–17 g/l) and immunoglobulin M (IgM) 0.2 g/l (normal value 0.4–2.3 g/l)). He is therefore substituted intravenously with immunoglobulins and albumin at intervals. In the course of severe protein loss enteropathy, endoscopic lymphangiography with embolisation of the lymphatic vessels was performed but did not show any long-term clinical improvement.¹⁵

The patient had received the vaccinations recommended by the German Standing Commission on Vaccination for his age group. Because of the complex anatomy, high levels of human leukocyte antigen (HLA) antibodies after several operations and multiorgan involvement in Fontan-like circulation, heart transplantation is no longer a feasible option.

Our patient was given 4 doses of Gamunex at > 20 intervals between 0.3 and 0.6 g/kg, and he also received an infusion of albumin 20% (1.2 g/kg/BW) in the context of symptom control management. Even for a patient with ventricular failure in a Fontan circulation, repeated infusion of immunoglobulins is not a risk factor. This volume is administered continuously over 4–8 hours. A volume overload is almost entirely ruled out due to the long administration. In addition, we treat patients with a single dose of 0.5 mg/kg furosemide to prevent the possibility of volume-associated side effects.

Before the administration of the IgG/albumin, IgG titres against measles, mumps, and rubella were determined: the patient's serum demonstrated a positive result for anti-measles IgG and anti-rubella IgG, while the result for anti-mumps IgG was negative. After administration of the iv-therapy, the lacking antibodies were replenished, and there was a positive test result in the enzyme-linked immunosorbent assay (ELISA) and the neutralisation test (NT) for mumps.

Serum samples were analysed by NT and ELISA. Anti-measles, mumps and rubella IgG titres were determined by anti-measles virus-ELISA (IgG), anti-mumps virus-AT-ELISA (IgG) and anti-rubella virus-ELISA (IgG) (all from Euroimmun) using an automated processor (Analyzer I-4P; Euroimmun).¹⁶ Titres were interpreted according to the manufacturer's instructions. The pre-treatment serum results were 428.5 mIU/ml (positive) for measles-IgG, 14.8 IU/ml (positive) for rubella IgG, and 2.28 RU/ml (negative) for mumps-IgG. The serum sample taken after the human immunoglobulin

(hIG) treatment showed a marked increase in IgG concentration for all three parameters (2952.7 mIU/ml (positive) for measles-IgG, 116.4 RE/ml (pos) for mumps-IgG, and 121.4 IU/ml (positive) for rubella-IgG.

Measles and mumps foci reduction neutralisation test was performed as described earlier.^{16,17} Briefly, serum samples were diluted serially, incubated with a constant number of plaque forming units of the respective virus, cultivated under a semi solid overlay, and stained plaques counted after 3 days. The neutralising capacity of the before and after treatment serum samples of the patient was calculated using the Kaerber formula. Prior to Gamunex application, the titre for measles neutralising antibodies was 1 >= 64 (positive) and 1 <= (negative) for mumps. After hIG transfusion, the neutralising capacity was positive and significantly increased with titres as 1 >= 256 for measles and 1 >= 128 for mumps. The Gamunex lot that was used for this patient was tested by foci reduction neutralisation test. The concentration of measles-neutralising antibodies was 1679.5 and that for mumpsvirus-neutralising antibodies 1 <= 500.

Discussion

Our case report describes a critically ill patient with a failing reverse 1 ½ palliation (failing Fontan-like circulation) who has been suffering from protein-losing enteropathy for several years. For such patients, heart transplantations may be the only feasible option if there are no contraindications, such as multiple organ failure or HLA antibodies. However, prior to surgery and the subsequent immunosuppression, the immune status with respect to live-attenuated vaccines must be checked and, if necessary, completed. In immunosuppressed patients, this is usually done via IgG titre determination. A subsequent neutralisation test may refine these results, since ELISA relies on the interaction of the antibodies with the antigen regardless of their neutralisation capacity while the neutralisation assay is a functional test.¹⁸ Neutralisation assays are considered the “gold standard” for determining protective immunity. In our patient, the immune status against measles, mumps and rubella was tested. Interestingly, the patient was seropositive for measles and rubella but not for mumps.

Protection of patients who will receive immunosuppressants is an important issue. As early as 2010, Urschel *et al.* described loss of various vaccine-induced antibodies after heart or heart–lung transplantation in children. Therefore, they recommend close adherence to vaccination schedules before transplantation, as well as a review of vaccine-specific antibodies after transplantation.¹⁹

Magdo *et al.* described in 2015, for the first time, immune abnormalities in Patients with a Fontan-associated-protein-losing enteropathy. All patients with a protein-losing enteropathy had a lymphopenia in addition to 25% of the control group of Fontan patients without a protein-losing enteropathy. Most of the patients 62.5% had negative titres for rubella, measles, and mumps compared to Fontan patients without a protein-losing enteropathy, who all showed positive titres for measles, mumps, and rubella.²⁰

Because of the isolated mumps antibody loss in our patient, we are now faced with further questions. Is it just a coincidence that isolated mumps antibody loss occurs in this patient? Can regular administration of immunoglobulins restore sufficient vaccine protection or should vaccinations be repeated? These questions should be further investigated in failing Fontan patients in the future.

The question, why we have in this case only a negative result for anti-mumps IgG, we cannot answer this question sufficiently with the underlying information. However, we aim to answer these questions through a further clinical study. This study should include more patients in order to answer these and other questions about immunological tolerance in failing Fontan. Especially in view of a potential heart transplantation, this is an interesting finding, which shows that the sole evidence in a vaccination certificate is not sufficient for the complex patients with a failing Fontan situation. Vaccinations are, in general, recommended for patients with a univentricular heart. Especially since this patient group often requires a heart transplant. Adequate immunisation is therefore of exceptional importance for these patients. Vaccination with measles mumps rubella and varicella is recommended from our point of view.

With this case report, we have demonstrated, as Magdo et al.,²⁰ that intermittent immunodeficiency for mumps is possible in the case of protein-losing enteropathy and should be monitored. Since congenital heart failures and Fontan circulation make it even more important to check that patients are protected from serious infections, like measles, rubella and mumps, we want to underline, that this type of investigation deserves attention. Testing should be performed with a standard ELISA in first line. If the results are negative, a neutralisation test might give more accurate information, since this is the gold standard for determination of the protective correlates against measles, mumps, and rubella.

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