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Anaesthesia and Orphan Diseases: Anaesthetic Management of Patient with Dock-8 Syndrome-8 Mutation

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Letter to Editor

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Letter to Editor

Dedicator of Cytokinesis 8 (Dock 8 Syndrome) Deficiency, described for the first time in 2009, is a rare condition which is caused by loss of function in DOCK8 encoding a guanine nucleotide exchange factor highly expressed in lymphocytes that regulates the actin cytoskeleton, MyD88-dependent Toll-like receptor signalling and the activation of the transcription factor STAT3. In other words, it is caused by homozygous or compound heterozygous deletions and point mutations in the DOCK8 gene (9p24.3) that is, an absence of DOCK8 protein in both, B and T lymphocytes. It is associated with consanguineous populations and, due to globalization; it is extending around the world. Analytically, it is translated as lower count of lymphocytes, very high levels of serum IgE (although a case with normal levels has been described) and moderate eosinophilia. As it affects immune cell migration, function and survival, this disorder impacts on innate and adaptive responses. Clinically, DOCK8 expresses susceptibility towards infections (herpes simplex virus infections, flat and verrucous warts , cytomegalovirus, Epstein Barr Virus, Rotavirus, Hepatitis A, B and C viruses, Staphylococus aureus infections or abscesses, otitis externa and nail and mouth candidiasis), bacterial or fungal infections have been described in the skin, liver, kidney, lung and brain with a broad spectrum from disseminated candidiasis to invasive Aspergillosis and Cryptococcus Neoformans as well as malignancy virally-driven up to 17% of patients (papillomavirus or molluscom contagiosum may develop anal, facial and vulvar squamous cell dysplasia and carcinoma). Nevertheless, other tumors have been identified as micro-cystic adrenal carcinoma and aggressive cutaneous T cell lymphoma.

Autoimmunity and allergic inflammation: atopic dermatitis, recurrent upper and low respiratory tract infections including otitis media, recurrent sinusitis, asthma, bronchitis, atelectasis, pneumonia and food environmental serious allergies. Patients' skin presents recurrent viral and bacterial infections. Other no cutaneous viral infections are: meningitis, encephalitis, keratitis, retinitis, blepharoconjuntitis, periodontitis, hepatitis and enteritis. Sclerosing Cholangitis has been described as a chronic manifestation of Cryptosporidium. Other intestinal parasitic manifestations can be seen such as, Endamoeba Histolytic and Giardia Lamblia. Malabsorption resulting in failure to thrive may well be caused by allergic or autoimmune enteropaty and intestinal infections. Also, chronic diarrhea can be attributed to enteropaty and it takes part of Hipper IgE Syndrome linked to X (IPEX-like disease). Another important digestive manifestation may be hypereosynophylic esophagitis [1]. Last but not least important, significant immune sequelae drives on hypothyroidism, vasculitis, autoimmune haemolytic aonemia, chorioretinitis and uveitis. Non-infectious Central Nervous System manifestations included vasculitis, aneurysms, tumor infiltration, strokes

and hemiparesis. At least 130 mutations have been identified and it is said that the cells which do not have DOCKS8, that is, T cells and natural killer cells (NK), are not able to maintain their shapes as they are crossing through dense spaces such as those found in the skin. Hence, the abnormal cells die and this explains why these patients have recurrent infections of the skin.

The explanation for the high levels of IgE, neurological symptoms and how this disease can affect the autoimmunity is lacking. Age of onset is neonatal or infancy and until 2017, 360 families have been found.

It is a severe autosomal recessive-combined immunodeficiency with a prevalence which is unknown, but being estimated about <1/1000000 and some patients present an immune Dysregulation, polyendocrinopathy, entheropathy: X-linked (IPEX)-like disorder [2]. There are patients who do not have mutations so, to those who do not have mutations in the gen Dock8; genetics of this disorder is unknown.

It can be diagnosed by familiar medical history, eosinophilia, high levels of IgG and for whole amplification by reaction in chain of polymerase (PCR) of the exons of the gene and posterior sequencing through a blood sample drawn with ethilenodiaminatetracetic - acid (EDTA) or a card impregnated with a dried blood sample. Allogeneic Bone Marrow transplant may well be the definitive treatment for this disease and it might be curative. However, other treatments are monthly immunoglobulin intravenous infusion and intraregional injections [3]. We report some anaesthetic considerations about Dock 8 Syndrome in a 21-year-old, 45kgrs, 151cm Hungarian woman, American Society of Anesthesiologist (ASA) physical status III with Dock8 8 mutation, who was scheduled for visiting the operatizing-theatre several times due to teeth toallet and for injecting intralesional cidofovir inside the left upper lip recurrent herpes virus simple wound. We run across idiomatic barrier, the father speaks, writes and understands the Spanish language but the patient did not. Partners of a patient with an autosomal recessive condition do not generally have symptoms or signs of the disease. Albeit they have a copy of mutated gen. Written and informed consent for publication was obtained from the patient´s father.

The patient has been suffering from this condition since 2011, when she was diagnosed on familiar basis. A patient´s sister suffered from the same condition and underwent bone marrow transplantation with successful results.

The patient´s past medical history was an uneventful vaginal delivery. At the age of two, the patient was diagnosed of cerebral toxoplasmosis with sphastic residual right hemiparesis with brachial predominance, as a neurological sequel. Although the patient was continent, she was not able to stand up due to equinovarus right leg. A wheelchair was needed. She had Vancomycin allergy. Bronchiectasis, without current infections. Forced expiratory volume in one second (FEV1) was 54%. Tubulophathy on daily chronic potassium treatment. Every fifteen days, endovenous immoglogulins and topical cidofovir were administered to the patient at day-hospital. She was on the following treatment: Baclofen® 5 milligrams (mgrs) per day (p/d). Vitamin D 3000, one tablet p/d. Topiramato® 50mgrs (p/d). Trimethropin-Sulfamethoxasol 800/1600 mgrs twice per day (t/d). Herpesin® 400mgrs 1 tablet each six hours (e/6 h). Mycosist® 1 tablet p/d. Berodual® droplets, twenty droplets e/8h. Sumatrolin® 2 tablet e/8h. Zelitrex® 500mgrs e/12h. Kaldyum® 600mgrs 2 tablets e/12h. NaHCO3 one gram (1 gr) e/6h. Theopirex® 150mgrs t/d. Past medical admissions were for low tract respiratory infection, over infected herpetic gigivoesthomatitis and generalized epilectic crisis in 2018 and 2019. Past surgeries were cerebral byopsy and pyogenic granuloma in the upper left eyelid, both without incidences.

The patient was rejected for allogenic bone marrow transplantation because of an active infection, reactivation of cerebral toxoplasmosis. Cerebral biopsy performed in 2019: Toxoplasma gondii DNA was detected by nucleic acid amplification. Complementary assessment: EKG was unremarkable. Chest radiography was under the acceptable limits. Analytically: IgA, IgM, CD4, CD8 and NK deficits. Hyper eosinophilia.

Cerebral RMN: Progressive Multifocal Leukoencephalopathy. When I met this patient, I realised that I had to like her because I was born to love and to take care of her, every single day of my life. She reminded me of an orphan-pretty-sad baby girl. I felt her sadness. She inspired me. The patient smiled at me only once, and I made her perioperative assessment for five times. The patient´s tinny face was uglified making the airway assessment impossible. The patient was not able to open her mouth due to pain and an enormous herpes simplex wound disfiguration her upper left lip. Eating or drinking was impossible for her. In a sense, I interpreted that she knew what her disgraceful destinity was. Nowadays, I do not make her perioperative assessment. Nevermore. Because I feel my soul broken when I see her. How can I not love her if she is an “orphan” girl! Perioperative Assesment: Pearls of practice (What should you do). Seeking for bacterial, viruses and fungical screenings. In any case, isolation is a rule. Paying attention to nutritional status, as drugs should be triated according to it. For that reason, oral nutrition and proteic supplements have to be initiated as soon as possible, for easily cicatrisation. Revise the previous anaesthetic register, if any. Nothing by oral route, 8 hours before surgery and 6 hours for solids and liquids respectively: Prophylaxis

of bronchoaspiration. Aspiration may well occur.

Perioperative aonemia should be treated with iron and folic acid supplements and eritropoyetine must be considered, as well. Thrombocytopenia has to be treated (steroids, dapsone...). Asking for haematologist advice is so important. Blood products without irradiation, desleucozitation by crioconservation and filtered (cytomegalovirus positive) must not be employed. Human Polyvalent Immunoglobulin may be used. Because of the idiomatic barrier, father should enter the theatre until the patient falls asleep in order to have the best communication with the patient and explain what you are doing … Anxiety must not be permitted. Premedication and taking only the necessary chronic treatment. Padding and skin protection should be a concern, as the patient has a very delicate skin and hemiparesis. Active warm disposable devices should be considered according to surgery. Monitoring should include temperature (neuromuscular blockers), level of anaesthesia depth (end-tidal expired gas monitoring, Biespectral index (BIS) according to maintenance form of your anaesthetics choices) and blocker neuromuscular monitoring. Antibiotic prophylaxis, ever. Sterilization and Hygiene are the goals. The patient must take a shower before surgery emphazaising on cleaning folings areas. Teeth cleaning and oral rinse with Chorhexidine and a careful hair removal according to the operating site, are compulsory. Follow the prophylaxis thromboembolic guidelines and elastic media compressive stockings. Laringeal mask may produce laringeal oedema. The trachea must be carefully intubated with disposable devices Depending on surgical site, povidone iodine or Chorhexidine should been considered, as the last one is not suitable for oral, back , neck and head surgery. Hence, chlorhexide should be the rule when it is not contraindicated. If blood products are needed, take into account that these patients have a IgA and other deficits, notice it to the Blood Bank. Finally, in the Recovery Room patient has to be isolated and in company of her father and sister, staying there, the necessary time for full awake state and recovery. They should not be strolled around the hospital. Finally, early rehabilitation is required.

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