



Probable Hydrocephalus Decompensation after Immunization with Pentavalent Vaccine: Case Report and Literature Review

Descompensação provável de hidrocefalia após imunização com vacina pentavalente: Relato de caso e revisão da literatura

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Abstract

Keywords

- ▶ pentavalent vaccine
- ▶ hydrocephalus
- ▶ arachnoid cyst
- ▶ inflammation
- ▶ blood-cerebrospinal fluid barrier
- ▶ neuroendoscopy

There are several complications associated with immunization with the pentavalent vaccine. Most of them are mild reactions, of spontaneous resolution; however, though rare, serious and potentially-fatal adverse effects can occur. We report a case of acute intracranial hypertension syndrome in an infant with a previously-unknown suprasellar arachnoid cyst who developed acute obstructive hydrocephalus after immunization with the pentavalent vaccine. He underwent neuroendoscopic treatment, showing complete resolution of the condition. The present article aims to compare the activation of the immune system by the pertussis component of the vaccine and the mechanisms that hypothetically potentiated the pathological decompensation.

Resumo

Palavras-chave

- ▶ vacina pentavalente
- ▶ hidrocefalia
- ▶ cisto aracnoide
- ▶ inflamação
- ▶ barreira hematoliquórica
- ▶ neuroendoscopia

Várias são as complicações associadas à imunização com a vacina pentavalente (VP). Em geral, são reações leves, de resolução espontânea; entretanto, raramente podem ocorrer efeitos adversos graves, potencialmente fatais. Relatamos um caso de síndrome de hipertensão intracraniana aguda (HIA) em lactente portador de cisto aracnoide supraselar até então desconhecido, que desenvolveu hidrocefalia obstructiva aguda pós imunização com VP. Ele foi submetido a tratamento neuroendoscópico, e apresentou resolução completa do quadro. Este artigo pretende comparar a ativação do sistema imune pelo componente pertússis da vacina e os mecanismos que hipoteticamente potencializaram a descompensação patológica.

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Introduction

The pentavalent vaccine (PV), which prevents against diphtheria, tetanus, whooping cough, haemophilus influenzae type B infection and hepatitis B, was introduced in the Brazilian childhood vaccination schedule in 2012, and is generally administered to infants aged 2, 4 and 6 months.¹

According to the “Handbook for the Epidemiological Surveillance of Adverse Events after Vaccination” (*Manual de vigilância epidemiológica de eventos adversos pós-vacinação*),¹ published in 2014 by the Brazilian Ministry of Health, mild local and systemic adverse effects are common, usually between 48 and 72 hours after immunization. Symptoms such as low or moderate fever (in 4.1% to 58.8% of the cases), drowsiness (in 28% to 48.8% of the cases), loss of appetite (in 2% to 26.5% of the cases), vomiting (in 1.1% to 7.8% of the cases), irritability (in 2.6% to 85.8% of the cases), and persistent crying (in 0 to 11.8% of the cases) are some examples.^{1,2}

They mainly occur in children under three months of age and are usually treated according to guidelines, with medication administration. It may also be necessary to change the vaccine formulation in future immunizations to prevent new events.²

Despite the fact that its safety has been extensively tested, severe adverse effects may occur on rare occasions, which, if not treated properly, can cause lasting damage, such as severe postvaccination neurological complications: encephalitis, meningitis, myelitis, optic neuritis, Guillain-Barré syndrome (GBS), narcolepsy, and parkinsonism.³

Such adverse effects are also observed after the administration of several other vaccine preparations, such as Bacille Calmette–Guérin (BCG), influenza hemagglutinin 1 and neuraminidase 1 (H1N1), *H. influenzae*, the human papillomavirus (HPV), and diphtheria, tetanus and pertussis (DTP).³

There are no specific studies on the complications after the administration of the PV; however, there are studies^{1,4} which mention the occurrence of complications after the administration of the in the DTP and tetravalent vaccines (DTP + *H. influenzae* type B conjugate).

Severe postvaccination complications include hypotonic hyporesponsive episodes (1/1,750 cases), convulsive crises (1/5,266 cases), apnea, anaphylactic reactions, and postvaccinal encephalopathy (0 to 10.5 cases per million doses administered).^{1,4}

Among the serious post-vaccination complications, those involving central nervous system (CNS) manifestations will be highlighted, as well as a discussion about the immunological mechanisms possibly involved in its genesis.^{5–8}

Since the most frequent adverse effects after vaccination are mild and sometimes nonspecific, they could be confused with the symptoms observed in the early stages of acute intracranial hypertension (AIH, such as irritability, crying, drowsiness etc.), especially in infants with compensated hydrocephalus of which the parents and pediatricians are unaware, causing undesirable diagnostic delays.^{9–11}

Although there are privileges regarding the protection of the CNS from unwanted immune processes, in the case herein reported, we noted that there was decompensation

of a preexisting and previously unknown neurosurgical condition, potentially harmful if not treated, emphasizing the need for a better understanding of the inflammatory postvaccine response over the blood-cerebrospinal fluid barrier (BCSFB).^{12–14}

The present article aims to report a case of acute obstructive hydrocephalus in an infant after immunization with the PV, and to discuss the possible mechanisms related to the immune response and BCSFB dysfunction.

Case Report

A male infant aged 6 months and 22 days was brought by his parents to the emergency room 3 days after the immunization presenting irritability, crying, profuse vomiting, and apparent visual loss.

His mother reported that the symptoms had already occurred on the first day after the application of the PV. He started with irritability and a high fever (38.5° C), which was controlled with the use of antipyretics.

The infant was previously healthy. He had no comorbidities, no history of allergic or vaccine reactions, presented neuropsychomotor development that was adequate for his age group, had been exclusively breastfed until the sixth month of life, and his vaccination booklet was up to date.

A physical examination revealed macrocrania (head circumference of 46 cm/greater than the 97th percentile) not previously reported in childcare consultations, and sensorineural impairment characterized by drowsiness and frequent vomiting. Signs of meningeal irritation were present, denoted by a tense anterior fontanelle +/4+, Kernig sign, and mild opisthotonus. The discreet presence of the sign of Parinaud drew attention.

At the pediatrician's request, a brain magnetic resonance imaging (MRI) scan was performed in the emergency room, under sedation and with anesthesiological follow-up. An evaluation by the neurosurgeon was requested because acute obstructive hydrocephalus with a lesion suggestive of suprasellar arachnoid cyst was evidenced (–Figure 1).

The lesion had an important extension to the cavity of the third ventricle, obstructing both the outflow tracts of the lateral ventricles and the opening of the cerebral aqueduct. The fourth ventricle had usual dimensions.

On magnetic resonance imaging of the brain, no signal alterations were observed in the brain parenchyma, or uptake by paramagnetic contrast in any of the sequences performed, and encephalitis could be excluded at first.¹⁵

With the parents' agreement, an emergency neuroendoscopy was chosen, without previous collection of cerebrospinal fluid (CSF). Although rare, the risks of further deterioration of the sensorium due to descending herniation (after the lumbar puncture) or the occurrence of intraventricular hemorrhage (after the transfontanelar puncture) were considered.^{16,17}

The CSF collection was performed at the time of ventricular puncture, through the endoscopic system, in a satisfactory manner. The possibility of placing an external ventricular shunt (EVS) at the same operative time or later, in case of

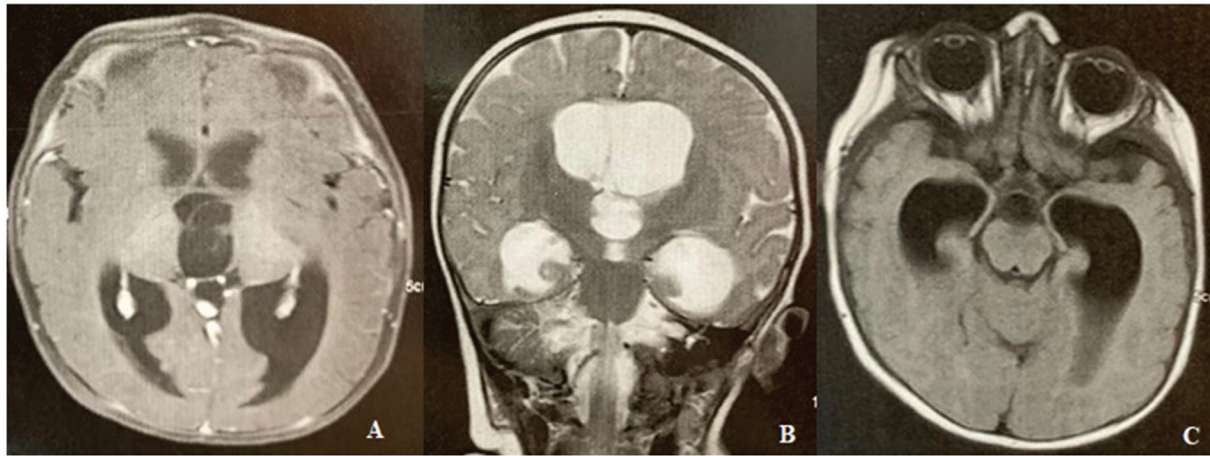


Fig. 1 Preoperative cranial magnetic resonance imaging (MRI) scan showing a cystic lesion in the suprasellar region, obstructing the flow of cerebrospinal fluid (CSF) and causing obstructive hydrocephalus upstream. (A,C) Axial T1-weighted MRI of the skull. (B) Coronal T2-weighted MRI of the skull.

suspicion or proof of infectious etiology, was also explained.¹⁸

The infant underwent general anesthesia, with the head in a slightly flexed neutral position, eye protection, and a thermal blanket. Cefazolin was administered as a prophylactic antibiotic.

We opted for the classic access to the right lateral ventricle, opening at the Kocher point, with trepanation using a number 15 scalpel blade, collecting the powder and bone micelles to occlude the orifice created. Linear durotomy was performed without coagulation of the dural edges, using a Karl Storz (Tuttlingen, Germany) Deqc 0° endoscope for the ventricular puncture.^{19–22}

Upon entering the right ventricular cavity, a large cystic lesion occluding the foramen of Monro was evidenced. The cyst had several cotton-wool spots on its surface (→ **Figure 2**). Protein materials could also be observed floating inside the

ventricular cavity, which led us to assume a probable inflammatory reaction as an origin for the decompensation of the condition.^{11,23,24}

The cyst was fenestrated using microscissors and, when entering it, the floor of the third ventricle was visualized in detail. This was open and displaced by the lesion, as well as the various arterial and venous structures and pituitary stalk.

The lower portion of the Arachnoid Cyst was opened towards the Carotid Cistern with Fogart Balloon number 2. After its communication, the lesion collapsed onto the floor of the third ventricle, also providing the permeability of the cerebral aqueduct.

A meticulous closing of the planes was carried out, occluding the burr hole with the powder and bone fragments collected.^{21,25}

An additional contralateral approach was chosen with caution. When entering the left lateral ventricle, it is possible

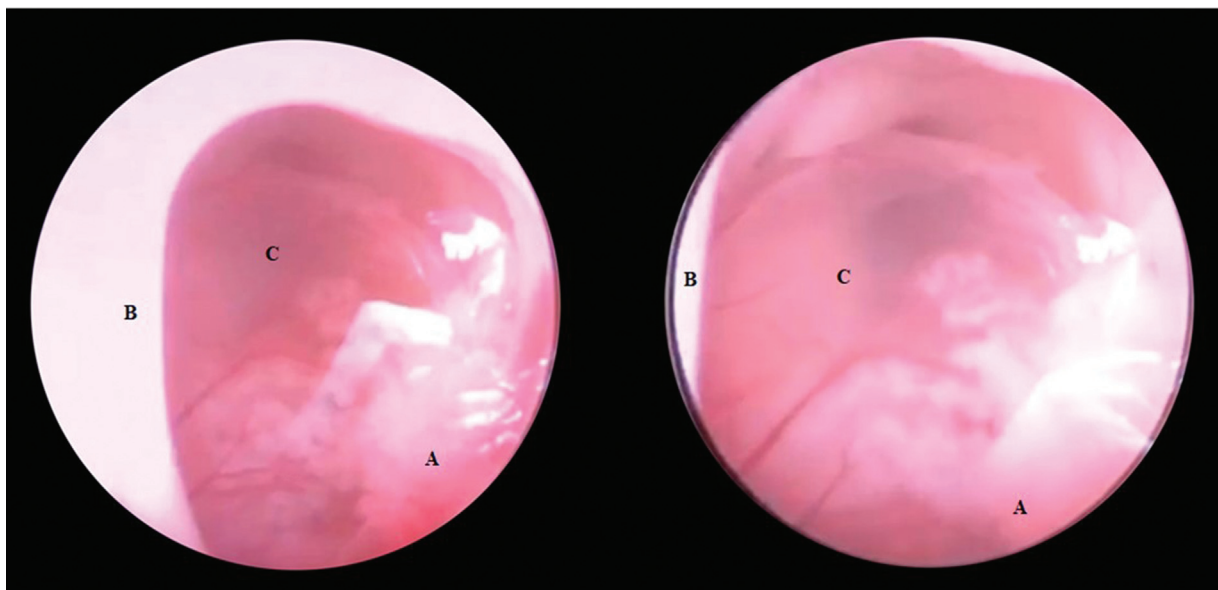


Fig. 2 Intraoperative view of the arachnoid cyst (C) occupying the ventricular cavity and covered by cotton-wool spots (A). Foramina of Monro (B).

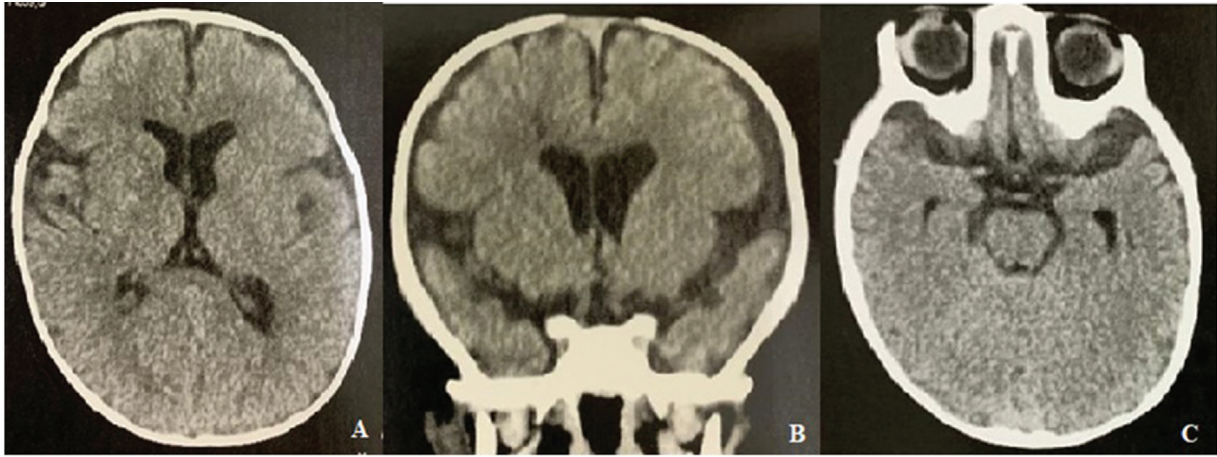


Fig. 3 Postoperative cranial computed tomography (CT) scan showing a reduction in ventricular cavities. (A, C) Axial section of skull CT. (B) Coronal section of skull CT.

to observe the total opening of the ipsilateral foramen of Monro. The cyst was completely collapsed, and was not submitted to resection, for we chose to interrupt the surgical procedure at this time. The same synthesis procedure was performed on the right side.

The patient was sent awake and responsive along with the mother to the Pediatric Intensive Care Unit, where, one day later, he was discharged to the ward without symptoms.²⁶

The analysis of the cerebrospinal fluid collected during the operation was performed. No alterations were observed in cellularity (8 cells / 100% lymphocytes) or in glucose (48 mg/dl), identifying only hyperproteinorraquia (80 mg/dl). Cultures did not demonstrate bacterial growth. Postoperative cranial tomography and brain MRI showed a significant reduction in supratentorial ventricular cavities (→ **Figure 3**, → **Figure 4**).

The large amount of particulate matter observed in the CSF and on the cystic surface led to the assumption of a inflammatory reaction, which may or may not be associated with vaccination. Classic works such as those by Spina-França and Saraiva²⁷ (1961) and Rocha et al.²⁸ (1971) have already reported the occurrence of leptomenigeal reactions in infectious and inflammatory processes and in aseptic causes.

Discussion

The neurosurgical pathologies that affect the sellar and suprasellar regions of children are varied. They comprise solid, cystic or mixed tumors, are most often histopathologically benign, but have a recognized potential for invasion of adjacent structures.²⁹

Examples of sellar and suprasellar lesions are craniopharyngeomas, pituitary adenomas, and optic-chiasmatic gliomas. Granulomatous lesions such as histiocytosis X, tumoral lesions derived from germ cells (germinomas), and cystic lesions secondary to defects of normal embryogenesis (Rathke cleft cysts) and arachnoid cysts may also be found more rarely.²⁹

Arachnoid cysts are benign lesions usually arising from a duplication of the arachnoid, but they can also have a rare posttraumatic etiology. They are filled with CSF, and comprise about 1% of all intracranial lesions. Sellar and suprasellar arachnoid cysts comprise 9% to 21% of these lesions. They usually predominate in men (with a ratio of 2:1), and their most frequent location is the middle fossa, representing about 50% of the cases.^{20,29,30}

Carriers of arachnoid cysts are mostly asymptomatic, however, in some patients they can become clinically manifest. These manifestations can range from simple paroxysmal headaches to severe cases of symptomatic intracranial hypertension.³¹

Focusing on the specific type of cyst in this report, of suprasellar location and extension to the cavity of the third ventricle, it is commonly manifested by obstructive hydrocephalus, visual alterations, endocrine alterations (short stature and delayed pubertal development), delayed neuropsychomotor development. Less frequently, seizures, head movement disorders (Bobbing Head Doll) and appendicular (tremors) may occur.²⁰

Several pathophysiological theories have been proposed to explain the symptomatology of these lesions. Some of them are the development of a valve mechanism, in which there is an imbalance between intracystic CSF inflow and outflow, intracystic CSF production, and an increase in the intralesional osmotic gradient due to an increase in the protein content.²⁹

There are different types of therapeutic approaches, from fenestrations (open, under microscopy or endoscopy with or without navigation) to derivations (cyst-peritoneum, cyst-subdural shunts), and they must be chosen on a case-by-case basis and depending on the structure of the service.^{20,31-33}

In the case in question, endoscopic fenestration of the cyst was chosen with satisfactory results. Furthermore, we believe that the increase in CSF protein content, both in the intraventricular and intracystic components, may have been the underlying cause of the decompensation and would be related to the recent immunization of the infant with cellular

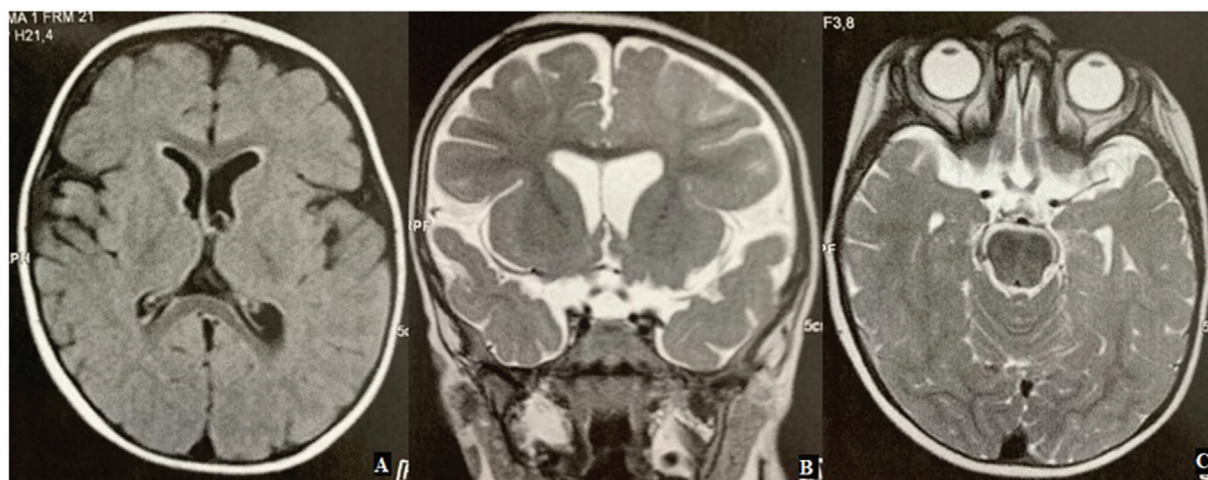


Fig. 4 Control skull MRI one year after the procedure, showing complete resolution of the pathology. (A) Fluid attenuated inversion recovery-weighted skull MRI in axial section. (B) Coronal T2-weighted MRI of the skull. (C) Axial T2-weighted MRI of the skull.

DTP, of recognized immunogenic potential, which will be detailed below.

Bordetella pertussis is a gram-negative bacterium that exclusively infects susceptible humans, causing pertussis, a respiratory disease that, in some cases, presents severe neurological complications. These are related to the antigenic components of the pathogen, mainly the pertussis toxin (TP), hemagglutinins, agglutinogens, adenylate cyclase, pertactin and tracheal cytotoxin.^{5,34-36}

In particular, PT causes ciliary paralysis of the airways due to exacerbated local inflammation. This leads to the accumulation of secretions and/or their inadequate removal, favoring secondary pneumonic processes (which can be severe, especially in the first six months of life).^{34,37}

Such inflammation leads to massive migration of lymphocytes, which are the first line of defense. Although the pathogenicity model is toxin-mediated, some bacteria can also be found in local macrophages, denoting tissue penetration.³⁴

Pertussis has an incubation period of 7 to 10 days, starting with a nonspecific cough and fever, similar to other infectious diseases of the airways. However, after about a week, the period of paroxysmal attacks of a characteristic (whooping) cough begins, which can last up to six weeks, causing great suffering to the patients and their families.^{1,37}

In uncomplicated cases, full recovery occurs within two to three months. Although pneumonic conditions are the most common complications, in 5.2% of all cases and in 11.8% of infants younger than 6 months, neurological complications such as encephalopathies can occur. These are severe conditions, worsened by hypoxia caused by airway obstruction, and a neuroimmune-mediated mechanism must be considered.^{2,35,37}

There are no animal reservoirs or vectors related to the transmission of pertussis, with humans playing an essential role in its life cycle. It is a highly contagious disease that can affect 80% of susceptible household contacts.³⁷

The mass immunization of communities played a crucial role in the reduction of the cases of pertussis. The first

“whole-cell” (cellular) pertussis vaccine was administered in the United States in 1914. Later, in 1948, it became associated with diphtheria and tetanus components, receiving the name DTP.³⁸

The DTP vaccine provides protective levels in 70% to 90% of the population immunized with four doses, but, due to the drop in levels of protective antibodies, it would need to be repeated every 10 years.^{4,35}

Due to the local reactions and adverse effects, an acellular DTP vaccine was developed, which purports to cause a lower incidence of adverse effects. However, the traditional DTP vaccine is still being used in several countries, including Brazil, where it is conjugated with two more components (constituting the PV), immunizing against *H. influenzae* and hepatitis B.¹

After immunization, the antigens present in VP, in particular those of the cell formulation, activate CD4+1 (Th1) T Helper lymphocytes that secrete cytokines such as Interleukin 2 (IL-2), Interferon γ and Tumor Necrosis Factor α (TNF- α).

These cytokines in turn promote the activation of CD4+ T Helper Lymphocytes 17 (Th-17) producing Interleukin 17 (IL-17), which seems to play a crucial role in the long-term post-immunization immune response and which is also related to the production experimental encephalomyelitis.³⁴

There are several proposed mechanisms for postimmunization CNS inflammation, with the granulocyte-macrophage colony-stimulating factor (GM-CSF) and the activation of T lymphocytes playing a crucial role in this process.^{6,39}

In experimental animal models, decreased GM-CSF activity was associated with reduced development of encephalomyelitis. The use of exogenous administration demonstrated an increase in the severity/onset of the condition. The GM-CSF is secreted by T Helper lymphocytes and induces microglial proliferation and activation.^{6,39}

Microglial activation increases the local production of oxygen free radicals, nitrogenous species, glutamate, TNF- α , neurotoxic phenotypic differentiation of microglia and an increase in pro-inflammatory mediators such as Interleukin-1B (IL-1B) and Interleukin-16 (IL-16).³⁹

The GM-CSF also contributes to the “break” of the BCSFB and to the recruitment of inflammatory cells from the peripheral blood. It also induces the proliferation of macrophages involved in the positive feedback of Th-1 and Th-17 cells.^{6,7,34}

The systemic inflammatory process postimmunization with the PV could decompensate hydrocephalus through a multifactorial mechanism related to the BCSFB.

The “break” of the BCSFB, which causes a higher concentration of proteins in the CSF, could increase the intracystic oncotic pressure. This would cause a slight increase in volume and secondary mechanical obstruction of the CSF drainage pathways.

The greater inflow of water through the BCSFB by diffusion would cause an unbalance in the cystic water inflow/outflow (valvular mechanism) which could also explain the deterioration of the patient’s clinical condition.¹⁴

The BCSFB differs from the blood-brain barrier (BBB) in several respects, but it is no less important. It has distinct regulatory and secretion mechanisms that give it great importance in the physiology and mechanical protection of the brain parenchyma. It is formed by the arachnoid and choroid plexuses and their interface with the cerebral cortex (convexity) and ependymal surfaces of the ventricular cavities.^{40,41}

The choroid plexuses are structures composed of highly-permeable capillaries and lined with a specialized epithelium that do not ultrafilter plasma CSF, but rather secrete it. They have microvilli that increase their surface and still receive differentiated irrigation, about ten times that received by the cerebral cortex.⁴²

In adults, the choroid plexuses produce about 600 mL of CSF daily, which shows the high “turnover” of the CSF. They not only help from a biomechanical point of view, protecting CNS structures by reducing their weight (floating effect), but they also have an essential metabolic role, as they carry micronutrients, peptides and hormones.⁴³

Their simple cubic epithelium has a basement membrane rich in type-IV collagen ($\alpha 3$, $\alpha 4$, and $\alpha 5$ monoclonal chains), and are similar to renal glomeruli in terms of selective permeability. They are rich in utrophin A, a transmembrane protein that provides structural stability and plays important roles related to cell signaling and homeostasis.⁴⁴

Choroid plexus cells capture HCO_3^- , Cl^- and Na^+ ions by active transport, and are rich in the number of mitochondria, endoplasmic reticulum and Golgi complex, mainly related to the secretion of products by transcellular transport.^{42,45,46}

The cells of the choroid plexuses have a modified apical surface, which is responsible for ion secretion via active transport (via apical Na^+ , K^+ , 2Cl^- cotransporters). This structure enables the passage of water through an osmotic gradient, regulated by mediated cellular transport channels such as aquaporin-1 (AQP1).^{42,45,46}

The passage of small proteins and other solutes by pinocytosis and/or exocytosis (transcellular transport) occurs on this surface.^{42,45,46}

Claudins 1, 2 and 11 proteins, especially Claudin 2 (CLDN-2), promote firm cell junction of this epithelium in the so-called occluding zone of the choroidal apical surface. Its genomic expression provides resistance to the cell surface, modulating inappropriate ionic exchanges and preventing larger molecules such as peptides, ferritin, and immunoglobulins from crossing the BCSFB.^{42,47}

The inflammatory response through TNF- α and interferon could negatively modulate CLDN2, enabling the disruption of the BCSFB, favoring paracellular transport, decreasing the selective permeability of the cell surface and increasing the protein content of the CSF.

The occurrence of an inflammatory reaction in the apical region and consequent dysfunction would promote inadequate modulation of ionic transport, enabling a greater ionic inflow into the CSF and the consequent increase in the passage of water through AQP1, resulting in an increase in CSF volume.⁴²

Thus, the immune and inflammatory effects caused by postPV immunization may have been the determining factors for the alteration of homeostasis, causing decompensation of the infant’s hydrocephalus.

Conclusion

Vaccination is crucial for the prevention of numerous infectious diseases. Despite its clear benefit, some patients may experience severe adverse reactions, especially when using preparations with greater immunogenic potential, such as the whole-cell pertussis component in the VP (cellular) vaccine.^{5,48}

In theory, the vaccine with the acellular pertussis component (DTPa) has a lower immunogenic potential. The DTPa immunizing agent is now used in all individuals in countries such as the United States, precisely because it provides similar protection and may lead to a reduction in serious adverse events.^{7,36,48}

Patients such as the one herein described, with a condition previously unknown to family members, could not have developed such a complication with the acellular vaccine formulation, and would have avoided emergency surgery due to harmful intracranial hypertension.^{4,5,35}

Further studies are suggested in patients with ventricular shunts (ventriculoatrial and ventriculoperitoneal) to understand if there is an impact of vaccination with the whole-cell pertussis component, a vaccine currently used in a large scale in Brazil, in the origin of malfunctioning valves.

Conflict of Interests

The authors have no conflict of interests to declare.

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