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Case Series Reports of Vaccination Induced Seizures with Encephalopathy in Paediatrics

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ABSTRACT

Vaccines save millions of lives every year, but patients who have an awful reaction to immunization may suffer from lifelong complications. Children are the most common victims of serious vaccine injuries. Febrile seizures and encephalopathy are two extremely rare vaccine-related injuries in pediatrics. In this case series discussion; an 18 months female child developed seizures and encephalopathy following the administration of the DPT (Diphtheria, Pertussis, and Tetanus) vaccine. The infant initially had a high-grade fever that did not respond to antipyretics, and all laboratory tests came back normal. In another case; a 17-month male child was admitted with a high-grade fever and two episodes of seizures following administration of MMR (Measles, Mumps, and Rubella) vaccine, DPT (Diphtheria, Pertussis, and Tetanus), OP (Oral polio) vaccine, JE (Japanese encephalitis) vaccine. He has diagnosed with sub-acute Sclerosing Pan encephalitis and was treated accordingly. In the third case; an 8 months female child was admitted with atypical febrile seizures following the administration of the MMR (Measles, Mumps, and Rubella) vaccine. MMR vaccine can produce febrile seizures in children with genetic variations in the genes **IFI44L** and **CD46**. CD46 has already been identified as a measles binding site**.** The routine immunization consists of a DPT vaccine with a whole-cell fraction of pertussis that is associated with neurological complications like seizures, encephalopathy, and hypotensive episodes. It is better advisable to use inactivated components of pertussis fraction instead of using the whole-cell vaccine.

INTRODUCTION:

As per WHO, a vaccine is a biological preparation that stimulates the body's immune system and improves immunity to a particular disease. Immunization is a process, where a person's own immune system is stimulated by which a person is made resistant to infectious diseases. Seizures that are caused due to fever are called Febrile seizures.[1] Most febrile seizures occur between the age of 6 months to 3 years of age with the peak incidence at 18 months. Febrile seizures are generally divided into two types, simple and complex. A simple febrile seizure comprises of generalized tonic-clonic activity without focal features of less than 10 min duration, without a recurrence in the subsequent 24 hr and resolving spontaneously. Complex febrile seizures are defined as one or more of the following features: a partial (focal) onset or showing focal features during the seizure, prolonged duration (greater than 10–15 min), and recurrent within 24 hr or the same febrile illness.[2] Encephalitis is inflammation of the brain that occurs when a virus directly infects the brain or when a virus or something else triggers inflammation. Encephalitis can occur in the following ways: A virus that caused an infection in the past becomes reactivated and directly damages the brain. A vaccine provokes a reaction that pressurizes the immune system attacks brain tissue (an autoimmune reaction). The most persistent neurological complication of measles virus infection is encephalitis. Primary measles encephalitis, acute post-measles encephalitis, measles inclusion body encephalitis, and subacute sclerosing panencephalitis are the four kinds of measles-induced encephalitis. [3]

Primary measles encephalitis:

In this condition, the brain becomes infected during the rash phase of the infection. The primary mechanism of infection is unclear, but onset at the early phase suggests a primary viral invasion of neurological cells followed by chemo-kine induction and lymphocytic infiltration.[4]

Acute post-measles encephalitis:

It has been proposed that acute post-measles encephalitis develops by molecular mimicry.[5] A circulating antibody reacts with a myelin protein, causing CNS dysfunction. As well as the typical symptoms of encephalitis, these patients may also have disturbed vision, difficulty in urinating, and hyporeflexia.[6]

Measles inclusion body encephalitis:

Measles virus is persistently present and the T-cell mediated hypersensitivity morbilliform rash does not develop or is minimal due to impaired T-cell function.CSF analysis appears normal at first glance, albeit modest pleocytosis and increased protein levels may be present. Levels of measles-specific antibodies in the CSF rise as the disease progresses. Following a biopsy, measles viral RNA can be reliably found in brain cells.[7]

Sub-acute sclerosing panencephalitis (SSPE):

It is thought that there is a failure to completely clear the virus following acute infection often in the first 2 years of life and the virus mutates, resulting in persisting and worsening infection.[8]

Clinical stages of SSPE:[9]

Stages	**Changes due to SSPE**
Stage 1	Behavioral decline, (lethargy, inattention, or temper-tantrums) and cognitive decline
Stage 2	Myoclonic jerks, seizures, and dementia
Stage 3	Rigidity, extrapyramidal symptoms, progressive unresponsiveness
Stage 4	Coma, vegetative state, autonomic instability, and akinetic mutism

Encephalopathy manifests with alteration of sensorium or generalized or focal seizures that persist for more than a few hours. The occurrence of hypertensive-hyporesponsive shock or post-vaccination encephalopathy is a contra-indication of further doses of the pertussis component.[10] The pertussis fraction of the DPT vaccine is responsible for this reaction. It is suggested that the acellular pertussis vaccine should be used instead of the whole-cell vaccine because it is associated with a lower frequency of neurological complications, such as seizures, encephalopathy, and hypotensive episodes. Naranjo's scale showed that the relationship between DPT and acute encephalopathy was probable. It causes neurologic damage: by affecting cellular signaling, catecholaminergic and GABAergic systems, and causes defects in the blood-brain barrier due to endotoxin-mediated endothelial damage. An acellular pertussis vaccine (designated as AP) is now available in several countries, including India. It contains purified, inactivated components of *Bordetella pertussis*. It is as potent as the whole-cell vaccine.[11]

CASE REPORT - 1

An 18 months old female child weighs about 9 kg, was brought to the PICU (Paediatric intensive care unit) of Gandhi Hospital, Secunderabad on 15/11/19 at 05:00 pm with chief complaints of high-grade fever which is continuous throughout the day that did not relieve on taking medication and also one episode of GTCS (Generalized Tonic-Clonic Seizure) which lasted for 3 min associated with up-rolling of eyeballs, deviation of the mouth and tonic-Clonic movements of upper limbs and lower limbs. History revealed that the child was immunized with DPT vaccine on the same day and there were no similar complaints in past.

On examination the child was drowsy, afebrile, pulse rate was found to be 102 beats/min. The respiratory rate was found to be 24/min. Heart sounds were heard. Bilateral air entry was clear. Per abdomen was soft. Her Lab report indicates the. Blood group as O '+'ve. GRBS was found to be 120mg/dl. The Complete blood picture was found to be as follows: Haemoglobin – 9.3 g/dl, total RBC - 4.33 cells/mm3, Haematocrit – 28.8%, MCV – 66.5, MCH – 21.5, MCHC – 32.3, total WBC – 8.92 thousand cells/mm3, Platelets – adequate, Neutrophils – 63.9%, Lymphocytes – 29%, Eosinophils – 02%, Monocytes– 6%, Basophils– 1%. Serum sodium – 135 mEq/L, Serum potassium – 3 mEq/L, Serum chloride – 102 mEq/L, Blood urea – 25.63 mg/dl and serum creatinine - 0.29 mg/dl.

Initially, the child was treated with injection Midazolam (0.1 mg/kg) and the seizures were aborted. A loading dose of injection phenytoin (20mg/kg) i.e. 180mg in 20cc normal saline through intravenous route was administrated. A maintenance dose of 20 mg of injection phenytoin was continued twice a day in treatment. Tepid sponging was advised to control the excess body heat. The following medications have been prescribed on the day of admission and the next day:

IVF – ½ DNS @ 35 ml/hr

Paracetamol rectal suppository SOS

Syrup. Paracetamol 5ml PO BID (each ml=125mg)

Inj. Midazolam 0.9mg in NS IV bid

Tab. Clobazam 5mg PO bid

On the 3rd day, the child again experienced 2 episodes of seizure, and a fever spike was also present in the TPR chart with a pulse rate – 106 beats/min, respiratory rate – 26/min, cardiac sounds – positive, bilateral air entry – clear, per abdomen – soft.

Treatment was changed from Inj. Phenytoin to Syrup. Phenytoin 4ml (5ml=30mg) PO BID and Tab. Clobazam was stopped.

On day 6, the child had no fresh complaints of seizure but complains of vomiting, cough and high-grade fever was present; she was prescribed with following medicine:

Syrup. Cefixime (80mg/kg/day) 3.5ml PO BID (50mg/5ml)

Inj. Zofer (0.1mg/kg) 0.9mg IV SOS

Syrup. Ambroxol 2.5 ml PO BID (25mg/5ml)

Syrup. Phenytoin 5ml PO bid (25mg /5ml) BID

Syrup. Paracetamol 6ml PO TID (5ml=125mg)

Inj. Midazolam 0.9mg in NS IV SOS.

This same medication was continued on day 7 as well.

On days 8 and 9, there were no fresh complaints and the child was stable with heart rate – 128/min, respiratory rate –26/min, cardiac sounds – positive, bilateral air entry – clear, per abdomen – soft. The child was free from seizures episodes and thus planned for discharge, with the following discharge medications:

Syrup. Phenytoin 7ml PO BID

Syrup. Cefixime 3.5ml PO BID

Syrup. Paracetamol 6ml PO SOS

Syrup. Ambroxol 5ml PO BID

CASE REPORT - 2

In this case, a 17-month-old male child weighing about 8 Kg was presented to PICU (Paediatric intensive care unit) of Gandhi Hospital, Secunderabad on 10/10/2019 at 03:00 pm with chief complaints of high-grade fever at midnight followed by a GTCS type seizure one

episode in the midnight and second episode in the morning which lasted for 20 min; associated with up-rolling of eyeballs, deviation of angle of mouth to the right side, drooling of saliva from the mouth. On examination, the child was irritable and drowsy. Midazolam (0.1 mg/kg) IV was administered immediately and the seizures were aborted.

The history of the baby revealed that she was immunized 3 days back with DPT, MMR, OPV, and JE vaccines and then he developed high-grade fever, loose stools, and vomiting. Furthermore, an episode of seizure was also developed. There were no similar complaints in the past. The baby was treated in a private hospital and diagnosed as 'Toxic Leucoencephalopathy' with late restricted diffusion. He was treated with pro-biotic and with oral rehydration salts for loose stool, Ondansetron for vomiting, Phenytoin, and Levetiracetam for seizure. Additionally, the baby has been prescribed Methyl Prednisolone and Carnisure (Levocarnitine) for an acute condition. Once the condition was subsided child was discharged and went back home.

On examination, the child was conscious, temperature – normal, pulse rate – 130beats/min, respiratory rate – 46/min, Heart sounds – positive, Bilateral air entry – clear, per abdomen – soft. His lab tests show; GRBS – 160 mg/dl, Haemoglobin – 7.5g/dl, total RBC – was 4.37 mill/mm3, MCV – 64.8, MCH – 17.2, total WBC – 36.86thousandcells/mm3),

Platelets – 283thouscells/mm3 adequate, Neutrophils – 88.4%, Eosinophils – 00%, Monocytes – 6.5%, Basophils – 2%. Serum sodium – 133mEq/L, Serum potassium – 4mEq/L, Serum chloride – 99 mEq/L, Blood serum creatinine - 0.2 mg/dl. MRI report revealed an impression: Sub acute sclerosing pan encephalitis.

The child with prescribed a loading dose of Inj. Phenytoin (2.5mg/kg) i.e., 20mg in 20cc normal saline through the intravenous route, following which a maintenance dose of 20 mg BID was continued. Once the baby was stabilized, the following medications were prescribed:

IVF- ½ DNS 800ml @ 32ml/hr.

Paracetamol rectal suppository 170 mg pr SOS

Inj. Levetiracetam 80mg with 20 ml NS over 20min

Inj. Ceftriaxone 400mg IV BID (100 mg/Kg/day)

Inj. Midazolam 0.8mg in NS IV SOS

The same prescription was continued for 4 days as the baby did not develop any further complications. On the 5th day baby was fit to discharge with the following discharge medication:

Syrup. Paracetamol 6ml PO SOS

Syrup. Phenytoin 5ml PO BID

CASE REPORT – 3

In this case, 8 months old female child weighing about 8 kg was brought to the emergency room of Gandhi Hospital on 17/10/2019 at 02:00 pm with chief complaints of fever since morning and a seizure episode at 7 pm associated with up-rolling of eyeballs and frothing. On examination, the baby was conscious and febrile, Heart rate was – 120beats/min, Respiratory rate – 30/min, Cardiac sounds – positive, bilateral air entry – clear, per abdomen – soft. The history of the baby revealed that she was immunized with MMR vaccine and was prescribed Vitamin A yesterday. She was admitted to the Department of Paediatrics, Gandhi hospital, Secunderabad. Her lab investigations show the following values-

Haemoglobin – 11g/dl, total RBC - 4.92 cells/mm3, Haematocrit – 36.9%, MCV – 75, MCH – 22.4, MCHC – 29.8, total WBC – 14.08 thousand cells/mm3, Platelets – 333 thousand cells/mm3, Neutrophils – 81.9%, Lymphocytes – 10.2%, Eosinophils – 01%, Monocytes – 7%, Basophils – 2%. Serum sodium – 137mEq/L, Serum potassium – 4mEq/L, Serum chloride – 106 mEq/L, Blood urea – 30.28mg/dl and Serum creatinine - 0.23 mg/dl, Serum calcium – 8.0, Serum proteins – 6.0, Serum albumin – 3.48, GRBS – 84 mg/dl, Fluid protein – 7, Globulin – nil. There was no bacterial growth found in the culture sensitivity test of urine.

Initially, upon admission, the child was prescribed with Inj. Midazolam 0.8mg in NS IV BID, once the child was stabilized and free from seizures, she was further prescribed with following medications:

IVF – ½ DNS @ 32ml/hr

Paracetamol rectal suppository 80mg PR SOS

Syrup. Paracetamol 5ml PO QID

Tab. Clobazam 5mg PO BID

Inj. Midazolam 0.8mg NS IV SOS

On day 2, the child again had an episode of seizure at about 9.00 am associated with up-rolling of eyeballs and fever spikes. After which, Midazolam was administered immediately which made the child free of seizures. The same medication was continued for the next 6 days. On day 9, the child was conscious and coherent, the temperature was normal, Pulse rate was 96/min, Respiratory rate – 26/min, and no fresh complaints of seizure were reported. The baby was fit to discharge. During discharge the following drugs were prescribed:

Syrup. Phenytoin 3.5 ml PO BID

Syrup. Paracetamol 5ml PO SOS

DISCUSSION:

Encephalopathy is a rare complication of pertussis fraction. Several neurologic complications have been described with the pertussis vaccines, particularly with whole-cell vaccines. Vaccine encephalopathy is, in fact, an inherited genetic defect of the voltage-gated neuronal sodium channel gene. The whole-cell vaccines lead to acute encephalopathy, seizures, hypotonic-hyporeactive episodes, inconsolable crying, or anaphylactic reaction.[5] Although a convulsion after DTP immunization was formerly thought to constitute a contraindication to further doses, in some cases, especially if the risk of pertussis in the community is significant, more doses may be warranted. If a child has seizures following the first or second dose of DTP it is desirable to delay subsequent doses until the child's neurological status is better defined. [12] The pertussis component of the DPT vaccine is mainly responsible for neurologic reactions. It causes neurologic damage by affecting cellular signaling, catecholaminergic and GABAergic systems, and defect in the blood-brain barrier due to endotoxin-mediated endothelial damage. The whole-cell pertussis vaccine induces the IL-1β production in the hippocampus and hypothalamus of vaccinated animals. This leads to a decrease in the release of the inhibitory neurotransmitters- GABA and adenosine in the hippocampus and induces convulsive activity. The acellular type did not induce the IL-1β production.[13] The same was present in our 1st and 2nd cases, in which the baby developed seizures as a neurologic reaction. DPT vaccines may be preferred to DTwP vaccine in those children with a history of severe adverse effects following DTwP vaccines or children with neurological disorders.[14] MMR vaccine has been linked with a very small risk of febrile seizures. Some people may

experience swelling in the cheeks or neck. MMR vaccine rarely causes a temporary low platelet count, which can cause a bleeding disorder. Extremely rarely, a person may have a serious allergic reaction to the MMR vaccine. Anyone who has ever had a life-threatening allergic reaction to any other component of the MMR vaccine, should not get the vaccine.[15] In our case study, both 2nd and 3rd case was reported with high-grade fever and associated with seizure post-MMR vaccine exposure. Even though all of the instances were well-managed with anti-epileptic and antipyretic medications, it is critical for clinicians to remain on the lookout for vaccine-related neurologic or other consequences and report them to the appropriate healthcare specialists for improved patient care.

CONCLUSION:

The vaccine-related neurologic damage can cause teething troubles for children and their families. Parents must be informed about seizures during the first dose of the DPT vaccine and bring the baby immediately to a consultant physician. Based on our case report it can be concluded that the encephalopathy was induced after the administration of the DTwP vaccine. Moreover, the early recognition of encephalopathy is of paramount importance for initiating appropriate management to prevent further complications and timely diagnosis will help to start the therapy to recover fully from the seizure effects. Clinical pharmacists as healthcare members should be alert enough to identify such cases and report accordingly.

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CONFLICT OF INTEREST:

None declared.

Ethical Permission

Not required.

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Nil.

Informed Consent Form

Not taken.

ABBREVIATIONS:

DTP: Diphtheria, Pertussis, and Tetanus; **MMR:** Measles, Mumps, and Rubella; **OPV:** Oral polio vaccine; **JE:** Japanese encephalitis; **WHO:** World Health Organisation; **CNS:** Central Nervous System; **CSF:** Cerebrospinal fluid; **RNA:** Ribonucleic acid; **PICU:** Paediatric intensive care unit; **GTCS:** Generalised tonic-clonic seizure; **GRBS:** Generalized random blood sugar; **RBC:** Red blood corpuscles; **MCV:** Mean corpuscular volume; **MCH:** Mean corpuscular hemoglobin; **MCHC:** Mean corpuscular hemoglobin concentration; **WBC:** White blood corpuscles; **IVF:** Intravenous fluid; **DNS:** Dextrose normal saline; **@:** At the rate of; **SOS:** Si-opus-sit (whenever required); **Syp:** Syrup; **ml:** Millilitre; **Inj:** Injection; **PO:** Peroral; **BID:** Two times a day; **mg:** Milligram; **NS:** Normal saline; **Tab:** Tablet; **TPR:** Temperature pulse respiration; **kg:** Kilogram; TID**:** Three times a day; **QID:** Four times a day; **MRI:** Magnetic resonance imaging.

SUMMARY:

Every year, vaccines save millions of lives. Febrile seizures and encephalopathy are two extremely rare vaccine-related injuries in pediatrics. In this case series discussion; an 18 months female child developed seizures and encephalopathy following the administration of the DPT (Diphtheria, Pertussis, and Tetanus) vaccine. In the second case; a 17-month male child was admitted with high-grade fever and two episodes of seizure following administration of MMR (Measles, Mumps, and Rubella) vaccine, DPT (Diphtheria, Pertussis, and Tetanus), OP (Oral polio) vaccine, JE (Japanese encephalitis) vaccine. In the third case; an 8 months female child was admitted with atypical febrile seizures following the administration of the MMR (Measles, Mumps, and Rubella) vaccine. In children with genetic abnormalities in the genes IFI44L and CD46, the MMR immunization can cause febrile seizures. Routine immunization consists of a DPT vaccine with a whole-cell fraction of pertussis that is associated with neurological complications like seizures, encephalopathy, and hypotensive episodes. Instead of utilizing the whole-cell vaccination, it is preferable to employ inactivated components of the pertussis fraction.

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