CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I.REACTION INFORMATION

1.PATIENT INITIALS (first, last)	1a.COUNTRY	2.DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year
Unknown	India				29	M			

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data)

CUSHING'S SYNDROME (Cushing's syndrome (10011652), Cushing's syndrome (10011652))
- Recovering/resolving
Case level outcome :Recovering/resolving

This case, derived from a full text scientific literature study article, was received on 02-Sep-2019.

This case refers to a patient who experienced the event cushing's syndrome while on therapy with prednisolone (company suspect) for an unknown indication.

Case report: A 29-year-old male presented with 1 1/2 years of di-culty in perceiving the shape and texture of objects with his right hand associated with numbness. He developed problems with typing without looking at the keyboard. He had inability in performing complex calculations and word-finding and sentence construction errors. Three months after onset, he developed gradual right grasp

Cont...

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☒ OTHER MEDICALLY IMPORTANT CONDITION

II.SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

Prednisolone(Prednisolone)

20.DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
1 mg/kg	Oral

21.DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE

DRUG USE FOR UNKNOWN INDICATION[10057097 - Drug use for unknown indication]

18. THERAPY DATES(from/to)	19. THERAPY DURATION
- Ongoing	

III.CONCOMITANT DRUG(S) AND HISTORY

22.CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

mycophenolate mofetil(mycophenolate)	3 g/day
Methylprednisolone(Methylpred-nisolone)	1000 mg/day

Cont...

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Concurrent Disease:
ATYPICAL RASMUSSEN'S ENCEPHALITIS[10071141 - Rasmussen encephalitis]
DIFFICULTY IN PERCEIVING THE SHAPE AND TEXTURE OF OBJECTS WITH HIS RIGHT HAND[10039994 - Sensation loss]

Cont...

IV.MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

VistaPharm, Inc.
Pharmacovigilance
7265 Ulmerton Road, Largo
Florida (FL) 33771 United States of America

24b. MFR. CONTROL NO.: VER201909-000972(0)

24c. DATE RECEIVED BY MANUFACTURER: 02/SEP/2019

24d. REPORT SOURCE: ☐ STUDY ☒ LITERATURE ☐ AUTHORITY ☒ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT: 11/AUG/2020

25a. REPORT TYPE: ☒ INITIAL ☐ FOLLOW UP

Literature Data :

Dash D, Garg D, Agarwal A, Mahajan S, Singh R, Bhatia R. Rasmussen's encephalitis presenting as progressive parietal dysfunction sans seizures. Seizure-Eur J Epilep. 2019; 71: 219-21.

Initial Reporter:
Deepa Dash
Department of Neurology,,
All India Institute of Medical Sciences,
New Delhi
India

Cont... = Continuation attached sheet(s)

DRAFT

Continuation Sheet for CIOMS report **Mfr. Control No. :VER201909-000972(0)**

Describe Reaction(s)(Include relevant test/lab data) (Cont...)

weakness. Over the next six months, he developed right-left confusion hampering driving. One year from onset, he developed right foot inversion while walking. All complaints were progressive. He had no headache, seizure, cognitive impairment, myoclonus, visual issues, prosopagnosia or systemic complaints. Family history was non-revelatory. Neurological examination at presentation to us 2 years from onset showed normal minimental state examination (MMSE) with impaired stereognosis, graphesthesia, hylognosis and two-point discrimination over the right upper and lower limb. Western aphasia battery revealed loss of fluency, occasional paraphasias and impaired repetition. He performed complex written calculations slowly but accurately. He exhibited mild right upper limb (power MRC grade 4/5) and right lower limb (MRC grade 3 to 4-/5) weakness. Right deep tendon reflexes were exaggerated. Remaining neurological and systemic examination was normal. Complete blood count, hepatic, renal and thyroid function were normal. HIV, HBsAg and Anti−HCV serology was negative. Magnetic resonance imaging (MRI) brain done six months apart revealed progressive atrophy hemiatrophy.

Cerebrospinal fluid (CSF) showed 15 cells (all lymphocytes), protein 85 mg/dL and sugar 108 mg/dL (blood sugar 145 mg/dL). Positron Emission Tomography (PET) brain revealed left frontoparietal hypometabolism. Electroencephalography (EEG) was normal. Antibodies for ANA, ANCA, Rheumatoid factor, anti-Thyroid Peroxidase, anti- Aquaporin 4 and anti-Myelin Oligodendrocyte Glycoprotein, autoimmune panel (including anti-NMDA, anti-VGKC, anti-GABA-A/B, anti- mGluR5, anti-AMPA, anti-GAD) were negative. Anti-measles antibody in CSF and serum was also negative. Anti-GluR3 antibodies are not available at our centre and could not be sent.

Based on these, a provisional diagnosis of autoimmune encephalitis or atypical Rasmussen’s encephalitis was entertained. He had empirically received intravenous immunoglobulins 2 g/kg over 5 days at an outside centre at onset, without improvement. He was not continued on immunomodulatory therapy. After evaluation at our centre, he was administered intravenous pulse methylprednisolone (1000 mg/ day) for 5 days followed by oral steroids (prednisolone 1 mg/kg). The patient did not give consent for brain biopsy at this time. The patient eventually consented and underwent brain biopsy three months from presentation to us from the left parietal lobe without complications. He had begun to show mild motor improvement around two months after the steroid pulse. Biopsy revealed changes consistent with RE. Mycophenolate mofetil was added as a steroid-sparing agent after the biopsy report and built up to 3 g per day with steroid taper, in view of steroid-related Cushing’s syndrome. The patient continued to exhibit steady improvement and was able to write and type without di·culty at last follow-up visit one month back.

Author's comment: The case report highlights a rare manifestation of a rare illness and adds to the growing repertoire of scientific knowledge regarding Rasmussen's encephalitis. The presence of progressive cognitive deficits in association with unihemispheric atrophy should strongly encourage clinicians to keep this diagnosis foremost to provide patients the benefit of immunomodulation.

Literature citation: Dash D, Garg D, Agarwal A, Mahajan S, Singh RK, Bhatia R, et al. Rasmussen's encephalitis presenting as progressive parietal dysfunction sans seizures. Seizure-Eur J Epilep. 2019;71:219-21.

Company's comment: Due to temporal relationship between administration of prednisolone and onset of the event "Cushing's syndrome" the World Health Organization (WHO) causality to prednisolone is possible.

Company Remarks (Sender's comments) (Cont...)

Company's comment: Due to temporal relationship between administration of prednisolone and onset of the event "Cushing's syndrome" the World Health Organization (WHO) causality to prednisolone is possible.

Suspect Drugs (Cont...)

Product-Reaction level

Seq.No. : 1
Drug : Prednisolone(Prednisolone)

Causality

1) CUSHING'S SYNDROME (Cushing's syndrome (10011652), Cushing's syndrome (10011652))
- Action(s) taken with drug : Dose Reduced
- Outcome after Change in dose : Unknown
- Outcome after reintro. of dose : Unknown
- Causality as per reporter (Drug/Vaccine) : Possible
- Causality as per Mfr.(Drug/Vaccine) : Possible
- Dechallenge : +ve
- Rechallenge : N/A

Concomitant drugs (Cont...)

Seq.No. : 1
Drug : mycophenolate mofetil(mycophenolate)
Indication for use : 1) DRUG USE FOR UNKNOWN INDICATION[10057097 - Drug use for unknown indication]

Causality

1) CUSHING'S SYNDROME (Cushing's syndrome (10011652), Cushing's syndrome (10011652))
- Action(s) taken with drug : Unknown
- Outcome after Change in dose : Unknown
- Outcome after reintro. of dose : Unknown
- Causality as per reporter (Drug/Vaccine) : Possible
- Causality as per Mfr.(Drug/Vaccine) : Possible
- Dechallenge : UNK
- Rechallenge : UNK

Seq.No. : 2

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Continuation Sheet for CIOMS report **Mfr. Control No. :VER201909-000972(0)**

Drug	:	Methylprednisolone(Methylprednisolone)
Route of Admin	:	1) Intravenous (not otherwise specified)
Indication for use	:	1) DRUG USE FOR UNKNOWN INDICATION[10057097 - Drug use for unknown indication]
Therapy Dates/Duration	:	1) 5 Days

Seq.No.	:	3
Drug	:	Immunoglobulins(Immunoglobulins)
Daily Dose	:	1) 2 g/kg
Route of Admin	:	1) Intravenous (not otherwise specified)
Indication for use	:	1) DRUG USE FOR UNKNOWN INDICATION[10057097 - Drug use for unknown indication]

Other relevant history (Cont...)

NUMBNESS[10029829 - Numbness]
RIGHT-LEFT CONFUSION HAMPERING DRIVING[10010300 - Confusion]
RIGHT FOOT INVERSION WHILE WALKING[10080134 - Foot inversion deformity]
GRADUAL RIGHT GRASP WEAKNESS[10076487 - Decreased ability to grasp]

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Additional information (continuation)

Laboratory data :

Neurological Examination: Normal minimental state examination (MMSE) with impaired stereognosis, graphesthesia, hylognosis and two-point discrimination over the right upper and lower limb. Western aphasia battery revealed loss of fluency, occasional paraphasias and impaired repetition.
Systemic examination was normal.
Anti-Myelin Oligodendrocyte Glycoprotein : Negative
anti-GABA-A/B, anti- mGluR5, anti-AMPA: Negative

Lab Result :

Test name	Test date	Test result	Normal value	Classification
ANA		Negative		
ANCA		Negative		
ANTI-AQUAPORI-N-4 ANTIBODY		Negative		
ANTI-GAD ANTIBODY		Negative		
ANTI-NMDA ANTIBODY		Negative		
ANTI-VGKC ANTIBODY		Negative		
BIOPSY		Changes consistent with RE		
BLOOD COUNT		Normal		
CSF CELL COUNT		15 cells (all lymphocytes)		
EEG		Normal		
HBSA		Negative		
HIV TEST		Negative		
INVESTIGATION		Anti-HCV serology was negative		
		108 (blood sugar) mg/dL		
LIVER FUNCTION TEST		Normal		
MEASLES ANTIBODY		CSF and serum was also negative		
MRI BRAIN		Progressive atrophy hemiatrophy		
NEUROLOGICAL		See Rel Lab		

Continuation Sheet for CIOMS report **Mfr. Control No. :VER201909-000972(0)**

EXAMINATION	Tests/Data
	Normal
POSITRON EMISSION TOMOGRAPHY	Left frontoparietal hypo- metabolism
PROTEIN	85 mg/dL
RENAL FUNCTION TEST	Normal
RHEUMATOID FACTOR	Negative
THYROID FUNCTION TEST	Normal
THYROID PEROXIDASE ANTIBODY	Negative

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