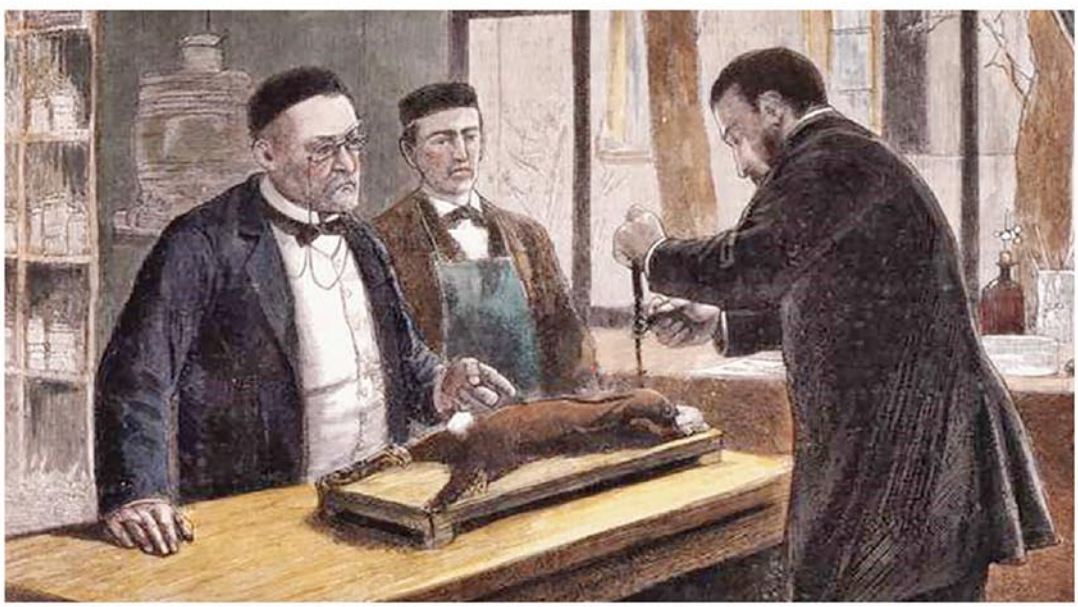
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Neurology & Internal Medicine

A Case-based Study



Ambar Chakravarty

Foreword
Jose Biller

JAYPEE

CONTENTS

Commentaries

Commentary 1: Neurological Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 1
Amit Halder, Ambar Chakravarty

Commentary 2: Seizures in Systemic Medical Illnesses 13
Joy D Desai

Commentary 3: Neurology and Renal Diseases 21
Ashis Datta

Commentary 4: Sepsis-associated Encephalopathy 27
Gautam Guha

Section 1: Tropical and Infectious Diseases

Case Series 1.1: Malarial Maladies

Case 1.1.1: Acute Inflammatory Demyelinating Neuropathy Following *Plasmodium vivax* Malaria 33
Ambar Chakravarty

Case 1.1.2: Cerebellar Ataxia Following *Plasmodium vivax* Malaria 34
Ambar Chakravarty

Case 1.1.3: Cerebral Malaria: A Peril of Enjoying Nature! 37
Ambar Chakravarty

Case Series 1.2: The Dengue Maladies

Case 1.2.1: Dengue Encephalopathy or Encephalitis-1? 40
Ambar Chakravarty

Case 1.2.2: Dengue Encephalopathy or Encephalitis-2? 40
Ambar Chakravarty

Case 1.2.3: Cranial Neuropathies in Dengue: Bilateral Facial Palsy 45
Ambar Chakravarty

Case 1.2.4: Cranial Neuropathies in Dengue: A Lady Who had Fever with Diplopia **46**
Ambar Chakravarty

Case 1.2.5: Dengue and Acute Neuromuscular Weakness **48**
Ambar Chakravarty

Case 1.2.6: A Cerebellar Syndrome in Dengue **50**
Ambar Chakravarty

Case 1.2.7: A Young Girl with Sudden Loss of Vision in Both Eyes and a Brain Hemorrhage **52**
Atanu Chandra, Mrinal Kanti Roy, Ambar Chakravarty

Case Series 1.3: The Chikungunya Malady

Case 1.3.1: When My Mom Developed a Foot Drop **55**
Ambar Chakravarty

Case 1.3.2: A Middle-aged Lady with Arthralgia and Sudden Visual Loss **56**
Ambar Chakravarty

Case 1.3.3: A Young Man with Facial Palsy and a Recent History of Fever with Rash and Arthralgia **57**
Ambar Chakravarty

Case Series 1.4: A Fatal Encephalitis and Rare Adverse Reaction to Vaccination

Case 1.4.1: A Classical Case **60**
Ambar Chakravarty

Case 1.4.2: A Classical Case…But with a Twist! **61**
Ambar Chakravarty

Case 1.4.3: An Unexpected Reaction! **61**
Ambar Chakravarty

Case Series 1.5: And the Mite Creeps On…

Case 1.5.1: A Case of Rhombencephalitis **68**
Sagar Basu, Siddhartha Chattopadhyay

Case 1.5.2: An Unusual Presentation of Scrub Typhus **74**
Sayonee Das, Ramiz Islam, Parvez Shahide Biswas, Sagar Basu

Case 1.5.3: Yet Another Unusual Presentation of Scrub Typhus **75**
Sayonee Das, Ramiz Islam, Parvez Shahide Biswas, Sagar Basu

Case 1.6: A Curious Case of Backache, Seizures, and Stroke **76**
Neetu Ramrakhiani, Vivek Vaid

Case 1.7: "Cutting the Gordian Knot"—A Tale of Deafness and Headache **82**
Neetu Ramrakhiani, Paresh Sukhani

Case Series 1.8: Neurotuberculosis—Some Uncommon Diagnostic and Therapeutic Challenges

Case 1.8.1: Recurrent Meningoencephalitis: Central Nervous System Infectious or Noninfectious Etiology? 88
Sangeeta Ravat, Shruti Agarwal

Case 1.8.2: Recurrent Meningitis: An Experience from the "Good Old Days"! 92
Ambar Chakravarty

Case 1.8.3: An Unusual Cause of Clinical Deterioration in Tuberculous Meningitis 94
Ambar Chakravarty

Case 1.8.4: An Unusual Cause of Higher Order Gait Disorder 97
Ambar Chakravarty

Case 1.8.5: CNS-TB-IRIS: A Neurologist's Nightmare! 100
Sarosh M Katrak

Case 1.9: A Rare Complication of Cryptococcal Meningitis 105
Sarosh M Katrak

Case 1.10: Pathogen is Nothing; The Terrain is Everything! 108
Subhash Kaul, Megha S Uppin

Section 2: Neurological Disorders during Pregnancy and Following Operative Procedures

Case 2.1: Hyperemesis Gravidarum with Encephalopathy 115
Ambar Chakravarty

Case 2.2: A Pregnant Lady with Altered Sensorium: A Revision!! 118
Kaushik Rana, Chaturbhuj Rathore

Case 2.3: A Pregnant Lady with Headache and Convulsion 123
Ambar Chakravarty

Case 2.4: Can PRES Occur without Pre-eclampsia? 128
Ambar Chakravarty

Case 2.5: Postpartum Headache: Role of Early Imaging 130
Ambar Chakravarty

Case 2.6: Weight Reduction may be Hazardous! 133
Ambar Chakravarty

Case 2.7: Vertigo Following Lumbar Spine Surgery 135
Ambar Chakravarty

Case Series 2.8: Neurological Complications of Surgeries Done Under General Anesthesia: Case Scenarios (Cranial Surgeries Excluded) 138
Ambar Chakravarty

Section 3: Puzzling Strokes

Case 3.1: All that Glitters is Not Gold!! 147
Jayanta Roy, Ambar Chakravarty

Case 3.2: Sam, I Have a Gut Feeling About this Aneurysm 150
Meera Viswanathan, Jia W Romito

Case 3.3: An Eponymous Syndrome: Its Diagnosis and Therapeutic Challenges 153
K Venkateswarlu, R Madan Mohan

Case 3.4: A Catastrophic Train Journey 158
Ambar Chakravarty

Case 3.5: A Devastating Episode in a Football Ground 162
Ambar Chakravarty

Case 3.6: Acute Lymphoblastic Leukemia Manifesting with Chemotherapy-induced Cerebral Venous Thrombosis 165
Madhu Nagappa, Sumanth Shivaram, Seshagiri Doniparthi V, Sanjib Sinha

Case 3.7: A Tale of Three Strokes: With an Intervening Twist 169
Barinder Singh Paul

Case 3.8: Not Really a Puzzle…A Very Rare Case Indeed!! 174
Ambar Chakravarty

Case 3.9: When a Hemorrhage Causes an Infarct 176
Praveen Kumar Yada, Subhash Kaul

Case 3.10: A Neurocardiac or Neuroendocrine Problem? 177
Sweety Tribedi, Ambar Chakravarty

Case 3.11: It's All due to Dereliction of the Power House 182
Mukul Malhotra, Karthik Muthuswamy, Maya Thomas

Case 3.12: Journey of a Diagnosis 188
Srimant Pattnaik, Biman Kanti Roy

Case 3.13: Fortune Favors the Brave: It's Never Too Late in CVST!! 192
Deep Das, Subhadeep Gupta

Case 3.14: Between the Devil and the Deep Blue Sea?? 195
Ambar Chakravarty

Case 3.15: Don't Overdiagnose Cerebral Venous Sinus Thrombosis!! 200
Ambar Chakravarty

Section 4: Neurohepatology and Unusual Posterior Leukoencephalopathies

Case 4.1: An Elderly Lady Having Difficulty in Performing Her *Puja* 205
Ambar Chakravarty

Case 4.2: A Middle-aged Man with Unsteadiness of Gait and Memory Loss 206
Ambar Chakravarty

Case 4.3: A Middle-aged Man with Alcoholic Liver Disease and Unsteadiness of Gait 206
Ambar Chakravarty

Case 4.4: The Brain, Liver, and Kidney Triumvirate 214
Yesica Andrea Campos, Venkatesh Ayagari

Case 4.5: Hyperammonemia in an Elderly Man in the ICU 217
Ambar Chakravarty

Case 4.6: Valproate-induced Hyperammonemic Encephalopathy 218
Ambar Chakravarty

Case 4.7: Valproate Hepatotoxicity–1 222
Ambar Chakravarty

Case 4.8: Valproate Hepatotoxicity–2 224
Ambar Chakravarty

Case 4.9: Hepatic Encephalopathy with Unusual Neuroimaging Features 226
Ambar Chakravarty

Case 4.10: A Most Unusual Case with PRES 227
Mrinal Kanti Roy, Ambar Chakravarty

Case 4.11: A Complex Case of PRES 229
Ramiz Islam, Sagar Basu

Case 4.12: And Yet Another Unusual Cause of PRES 233
Mrinal Kanti Roy, Arkaprova Chakraborty, Ambar Chakravarty

Section 5: Neurohematology and Paraneoplastic Syndromes

Case 5.1: A Young Lady with Immune Thrombocytopenia, Headache, and Visual Loss 239
Ambar Chakravarty

Case 5.2: "ALL" is not Well! 243
Venkatesh Ayagari

Case 5.3: From Bones to the Brain 247
Khalid Mohamed Ahmed, Kartavya Sharma

Case 5.4: A Child with a Hemorrhagic Mass in the Brain 250
Sandip Chatterjee, Mousami Mukherjee, Ambar Chakravarty

Case 5.5: A Rare Cause of Polyneuritis Cranialis 253
Mrinal Kanti Roy, SB Niroop, Ambar Chakravarty

Case 5.6: Painless "Bell's Palsy" in Children: Watch Out!! 256
Ambar Chakravarty

Case 5.7: Anhidrosis or Hyperhidrosis—That is the Question? 258
Ambar Chakravarty

Case 5.8: Yes Indeed…It is Hyperhidrosis!! 263
Sandip Chatterjee, Ambar Chakravarty

Case 5.9: Miller Fisher Syndrome or Chronic Inflammatory Demyelinating Polyneuropathy: While Neurologists Fight—The Culprit Smiles!! 265
Ambar Chakravarty

Case 5.10: Anchoring Bias 268
Faith N Good, Venkatesh Ayagari

Case 5.11: Burkitt Lymphoma Manifesting with Neoplastic Meningitis 273
Madhu Nagappa, Sumanth Shivaram, Seshagiri Doniparthi V, Sanjib Sinha

Case 5.12: Subacute Neuroregression in a Toddler: Worth Chasing the Hidden Culprit! 275
Sudhakar Karunakaran, Karthik Muthuswamy

Case 5.13: A Rare Differential of Statin-induced Myopathy 279
Ambar Chakravarty

Section 6: Movement Disorders

Case 6.1: Look Once…Twice…and Even More: Till You Find the Offender! 285
Sweety Trivedi, Ambar Chakravarty

Case 6.2: A Near Miss…Saved at the Last Moment! 290
Ambar Chakravarty

Case 6.3: Neurogenic Bladder in a Patient with Depression and Chronic Back Pain 291
Sanjay Prakash

Case 6.4: An Unusual Cause of Febrile Encephalopathy in a Migraine Patient 295
Sanjay Prakash

Case 6.5: A Truly Neuropsychiatric Problem! 300
Ambar Chakravarty

Case 6.6: A Girl Child with Proximal Muscle Weakness 303
Ambar Chakravarty

Case 6.7: An Emergency in Wilson Disease 308
Ambar Chakravarty

Case Series 6.8: The Saga of Spiky Red Blood Cells!

Case 6.8.1: Low Cholesterol?…Do not Be too Complacent! 312
Ambar Chakravarty

Case 6.8.2: A Fidgety Man Who Developed Eating Difficulty and Frequent Tongue Biting 314
Ambar Chakravarty

Case 6.8.3: A Complex Familial Disorder 316
Ambar Chakravarty

Case Series 6.9: Stridor in Neurology

Case 6.9.1: Just Heard It: But Could Not Save! 320
Ambar Chakravarty

Case 6.9.2: A Narrow Escape…God's Mercy! 321
Ambar Chakravarty

Case 6.10: Diabetic Striatopathy: A Movement Disorder Emergency 324
Sumanth Shivaram, Madhu Nagappa, Seshagiri Doniparthi V, Sanjib Sinha

Case 6.11: A Young Lady with Recent Onset of Abnormal Movements..., No! She was not Pregnant! 326
Ambar Chakravarty

Case 6.12: An Elderly Man with a Multitude of "Soft" Neurological Signs, "Soft" Radiology but "Hard" Genetics! 328
Ambar Chakravarty

Case 6.13: A Neurological or Endocrinological Problem? 330
Ambar Chakravarty

Case 6.14: A Bent Spine 332
Ambar Chakravarty

Case 6.14.1: Bent Spine: A Brief Note on a Mixed Problem 335
Ambar Chakravarty

***Appendix 1*: Head Drop/Head Ptosis** 336
Ambar Chakravarty

***Appendix 2*: Head Drop/Head Ptosis** 336
Ambar Chakravarty

Section 7: Neuroimmunology

Case 7.1: A Lady with Recurrent Vomiting **341**
Jui Jade, Bhim S Singhal

Case 7.2: Healed Thyself!! **344**
Sandip Chatterjee, Ambar Chakravarty

Case 7.3: Stopped at the Checkpoint **348**
Essie P Mathews, Jia W Romito

Case 7.4: Doctor's Agony…Colleagues Ponder!! **351**
Sandip Chatterjee, Ambar Chakravarty

Case 7.5: A Complex Problem: Rheumatoid Atlantoaxial Subluxation **353**
Sandip Chatterjee, Ambar Chakravarty

Case 7.6: Chronic Nasal Sinusitis and Pachymeningitis: Is there any Link? **356**
Seshagiri Donipathri V, Madhu Nagappa, Sumanth Shivaram, Sanjib Sinha

Case 7.7: A Young Lady with Super-refractory Status Epilepticus Due to Vasculitis **359**
M Ravindranath Chowdhary, Anita Mahadevan, Sanjib Sinha

Case 7.8: A Truly Multisystem Disease: A Synopsis of 20 Long Years of Suffering!! **363**
Debasish Roy, Ambar Chakravarty

Case 7.9: Stiff-person Syndrome: Immunotherapy is Rewarding! **367**
Sumanth Shivaram, Madhu Nagappa, Seshagiri Doniparthi V, Sanjib Sinha

Case 7.10: A Case of a Young Man with Uncontrolled Laughter, Hypersomnolence, and Cognitive Decline **372**
AS Girija

Section 8: Neuroendocrinology and Metabolic Disorders

Case 8.1: Beware of Too Much Net Surfing!! **379**
Sudip Chatterjee

Case 8.2: An Important Tip in Managing DKA **381**
Sudip Chatterjee

Case 8.3: Eyes Do Not See What Mind Doesn't Know!! **382**
Sudip Chatterjee

Case 8.4: Water…Water…Everywhere!! **384**
Sandip Chatterjee, Ambar Chakravarty

Case 8.5: The Vanishing Pituitary!! 389
Ambar Chakravarty

Case 8.6: Refractory Epilepsy? - Have a Look at the Hands!! 392
Sudip Chatterjee

Case 8.7: Epilepsia Partialis Continua: Thinking Out of the Box 395
Ambar Chakravarty

Case 8.8: A Stitch in Time Saves Nine! 398
Angshuman Mukherjee, Ambar Chakravarty

Case 8.9: Searching for a Treatable Condition may Provide a Glimmer of Hope for Patient and Doctor 402
Jimmy Lalkaka, Harsh Oza

Case 8.10: A Lady with Episodic Psychosis!! 405
Chaturbhuj Rathore , Kaushik Rana

Case 8.11: When a Hypoglycemic Patient Didn't Wake Up!! 410
Kaushik Rana, Chaturbhuj Rathore

Case 8.12: "Wonder - Drug" Masking Neurometabolic Disorder 414
Sangeeta Ravat, Rahil Ansari

Case 8.13: Too Fast and Too Furious 418
Claribel D Wee, Stephen A Figueroa

Case 8.14: Adding Salt to the Wound 421
Yoo-Jin Michelle Baik, Ranier Reyes

Section 9: Neuromuscular Disorders

Case 9.1: A Case of Refractory Demyelinating Neuropathy 429
Megha Dhamne, Riddhi Patel, Satish V Khadilkar

Case 9.2: Disease is a Sneaky Thief: Watch for Clues! 433
Riddhi Patel, Satish V Khadilkar

Case 9.3: Immune Modulation Therapy for Drug Induced Painful Neuropathy 437
Ambar Chakravarty

Case 9.4: POEMS Syndrome – A Revision: But More the Merrier!! 439
Sumanth Shivaram, Madhu Nagappa, Seshagiri Doniparthi V, Sanjib Sinha

Case 9.5: A Case of Subacute Bilateral Paresthesia with Deranged Liver Function Tests 442
Amy L Ross Russell

Case 9.6: What is the Cause of This Neuropathy? 445
Riddhi Patel, Satish V Khadilkar

Case 9.7: A Common Condition with an Uncommon Etiology 449
Ambar Chakravarty

Case 9.7.1: A Very Unusual Feature in a Case of Neuralgic Amyotrophy 451
Ambar Chakravarty

Case 9.8: Keep an Open Mind – Even if the Diagnosis is Written on the Face!! 452
Ambar Chakravarty

Case 9.9: An Unusual Case of Recurrent Neuromuscular Paralysis 454
Ambar Chakravarty

Case 9.10: What Would You Do When You cannot Wean a Myasthenic Patient Off the Ventilator? 457
Ambar Chakravarty

Case 9.11: A Rare Masquerade of a Neuromuscular Disease 460
Ambar Chakravarty

***Appendix*: Editorial Commentary: Some Pearls in Neuromuscular Diseases for the Internists** 463

Section 10: Rage of the Angel—One Hundred Years Later!!

Case 10.1: The Great Mask—Evader 467
Venkatesh Ayagari

Case 10.2: Severe Acute Respiratory Syndrome Coronavirus 2 and Stroke-1 470
Sweety Tribedi, Jyoti Bala Sharma, Atampreet Singh

Case 10.3: Severe Acute Respiratory Syndrome Coronavirus 2 and Stroke-2 472
Sweety Tribedi, Jyoti Bala Sharma, Atampreet Singh

Case 10.4: Severe Acute Respiratory Syndrome Coronavirus 2 and Stroke-3: Between the Devil and the Deep Sea! 476
Subhash Kaul, Anant Ram

Case 10.5: Severe Acute Respiratory Syndrome Coronavirus 2 and Stroke-4: A Brainstem Stroke 479
Ambar Chakravarty

Case 10.6: Severe Acute Respiratory Syndrome Coronavirus 2: Encephalitis or Encephalopathy? 482
Amit Halder

Case 10.7: A Case with Intermittent Abnormal Movements: Is It Severe Acute Respiratory Syndrome Coronavirus 2: Encephalopathy? 484
Amit Halder

Case 10.8: Long Haul COVID: New Onset of an Uncommon Headache Disorder Following Severe Acute Respiratory Syndrome Coronavirus 2 Infection 486
Ambar Chakravarty

Section 11: Uncommon Headaches and Orofacial Pains for the Internist

Case Series 11.1: The Saga of Giant Cell Arteritis

Case 11.1.1: An Elderly Man with an Intractable Headache 491
Ambar Chakravarty, Debasish Roy

Case 11.1.2: An Elderly Man Who Woke Up with a Headache and Visual Loss 492
Ambar Chakravarty, Debasish Roy

Case 11.1.3: Elderly Man with Headache and Double Vision 493
Ambar Chakravarty

Case 11.1.4: A Middle-aged Lady with Jaw Uneasiness 494
Ambar Chakravarty

Case 11.2: A Middle-aged Man with Headache, Visual Disturbance, and Recurrent Episodes of Confusion and Altered Sensorium 498
Ambar Chakravarty

Case Series 11.3: Tales of a Genetic Disease

Case 11.3.1: A Middle-aged Lady with Migraine with Aura and Rapidly Progressive Dementia 501
Ambar Chakravarty, Angshuman Mukherjee

Case 11.3.2: A Middle-aged Lady with Gait Instability and Incontinence 502
Ambar Chakravarty

Case 11.3.3: A Similar Case but with Something More...! 503
Angshuman Mukherjee

Case Series 11.4: An Uncommon Disease with Diverse Manifestations

Case 11.4.1: Middle-aged Man with Recurrent Headaches, Fever, Stroke-like Episodes, and an Iatrogenic Complication 509
Ambar Chakravarty

Case 11.4.2: A Young Lady with Intermittent Headaches, Stroke-like Episodes, and Abnormal Movements 513
Ambar Chakravarty

Case 11.5: A Middle-aged Lady with Intractable Headache 515
Ambar Chakravarty

Case 11.6: Another Lady with Intractable Headache and Similar Imaging Abnormality with a Definitive Diagnosis 516
Ambar Chakravarty

Case 11.7: The Lady Who Fooled the Surgeon! **519**
Ambar Chakravarty

Case 11.8: A Young Man with Acute Onset of Severe Headache, Atrial Fibrillation, and a Stroke-like Episode **522**
Ambar Chakravarty

Case 11.9: An Elderly Man with Severe Throat Pain Shooting up to Ipsilateral Eye and Temple with ANS Features Including Salivation **525**
Ambar Chakravarty, Angshuman Mukherjee

Case 11.10: A Man with an Intractable Abdominal Pain **527**
Ambar Chakravarty

Case Series 11.11: When Sex is a Headache!

Case 11.11.1: Headache in the Shower **529**
Ambar Chakravarty

Case 11.11.2: Sex Headache: May be a Very Serious Matter Indeed! **529**
Ambar Chakravarty

Case 11.11.3: Why You Need to Do Angiography Even in CT Negative Sex Headaches as Well! **530**
Ambar Chakravarty

Case 11.11.4: A Very Rare Cause of Headache Related to Sexual Activity **537**
Ambar Chakravarty

Case 11.12: A Curious Case of Headache in the Shower **540**
Ambar Chakravarty

Case 11.13: A Middle-aged Lady with Bursting Headache Following Micturition **542**
Ambar Chakravarty, Sagar Basu

Case 11.14: Yet Another Case of Thunderclap Headache **543**
Ambar Chakravarty

Case 11.15: An Elderly Man with Severe Left Facial Pain and a Miraculous Cure! **545**
Ambar Chakravarty

Case 11.16: A Middle-aged Lady with Intractable Left Facial Pain and Double Vision **549**
Ambar Chakravarty

Case 11.17: An Elderly Man with Facial Twitching and Burning Tongue **551**
Ambar Chakravarty

Section 12: Unusual Neurocutaneous Syndromes

Case 12.1: When the Skin is a Window to the Brain? 557
Aparajita Chatterjee, Madhu Nagappa, Sumanth Shivaram, Seshagiri Doniparthi V, Sanjib Sinha

Case 12.2: Indeed the Skin may be a Window to the Brain—But in a Slightly Different Way !! 560
Mousami Mukherjee, Ambar Chakravarty

Case 12.3: When the Eyes Say it All!!! 563
Aparajita Chatterjee, Madhu Nagappa, Sumanth Shivaram, Seshagiri Doniparthi V, Sanjib Sinha

Case 12.4: A Constellation of Several Anomalies: Where is the Missing Link? 566
Ambar Chakravarty

Case 12.5: A Young Girl with Sudden Loss of Hearing in Both Ears 570
Ambar Chakravarty

Case 12.6: A Very Rare Syndrome 574
Amit Halder, Ambar Chakravarty

Case 12.7: Unusual Presentation of a Not So Uncommon Syndrome 576
Ambar Chakravarty

Index 583

SECTION 4

Neurohepatology and Unusual Posterior Leukoencephalopathies

JAYPEE BROTHERS

CASE 4.1

An Elderly Lady Having Difficulty in Performing Her *Puja*

Ambar Chakravarty

CASE HISTORY

The author was called to see a 72-year-old lady (1988) rather urgently one morning because she could not perform her daily *Puja* ritual properly and got extremely upset at that. Her family members were equally anxious. Her daily morning *Puja* ritual consisted of chanting *stotras* for about an hour during which she would unfold and fold five pictures of various Gods and Goddesses, of sizes approximately 3 inches × 2.5 inches, all having a separate metal frame but hinged together. When folded properly, it would look like a book. While unfolding the pictures was relatively easy, folding them back needed a particular sequence to be followed. This lady, as a result of practicing for several years mastered the technique well and never experienced any problem either in unfolding the five pictures and at the end of chanting *strotras* or folding them back into place. On that particular day, although she could unfold the pictures properly, after the *Puja*, she could not fold them back into place even after several attempts and was very upset at that. She refused to have any help from other family members and feared that something untoward might happen in her family as God was probably unhappy with her. On direct enquiry, it was revealed that for about 1 month, she had not been feeling well, developed general weakness and lost her appetite. During examination, on being asked to fold the set of pictures, she was noticed to fumble with the picture frames; looking at that her son commented that it was most unusual for her to do the same as normally she could do the folding in proper sequence with no problem. Further examination revealed slight icteric tinge of her conjunctivae, mild hepatosplenomegaly, and an obvious flap in her outstretched and slightly extended hands. She was a bit unsteady on her feet and had depressed reflexes and flexor planters. She had no free fluid in her abdomen on clinical examination. She had no addictions. She was unable to draw a rectangular box, a bisecting pentagon, and was unable to construct a star with six matchsticks after she was shown by the author how to do that. Investigations revealed her total bilirubin to be 2.8 mg%, moderately raised transaminases and alkaline phosphatase (ALP), and a grossly altered albumin–globulin ratio (2.6:3.9). Abdominal ultrasound confirmed hepatosplenomegaly with heterogenous echotexture of the liver and presence of a small ascites. Her HBsAg (hepatitis B surface antigen) was negative. She was referred to a senior general physician, known to the family, for further management.

JAYPEE BROTHERS

CASE 4.2

A Middle-aged Man with Unsteadiness of Gait and Memory Loss

Ambar Chakravarty

CASE HISTORY

A 52-year-old hypertensive man presented with about 8-month history of progressive unsteadiness of gait, a few falls while turning, and recent onset of short-term memory loss. He had no problems with his upper limbs but had a little alteration in speech. His vision was normal and he had no addictions. He walked at a slow speed with a broad base and was seen to be particularly unstable while taking a turn when he shuffled quite a bit. He had some degree of symmetrical reduced swinging of hands while walking but had no tremor. He had no significant slowness of his hand movements. Muscle tone was increased, especially in the legs, and his ocular movements were full. Speech was a bit slurred, he was continent, but had some recent memory loss and some difficulty in doing simple calculations. He had moderate degree of hepatosplenomegaly, no ascites, or pedal edema. His liver functions were deranged with raised transaminases and alkaline phosphatase and grossly altered albumin–globulin ratio. Abdominal ultrasound and liver fibroscan confirmed cirrhotic changes in the liver with portal hypertension. His serum ceruloplasmin level was 20 mg% (within normal range). He was advised to have a magnetic resonance imaging (MRI) of brain.

Instead, his relatives took him to a different institution where his copper studies were repeated. Although his ceruloplasmin was again found to be normal, his 24-hour urinary copper excretion was found to be higher than the upper limit of normal. He had no Kayser–Fleischer ring. He was thought to have Wilson's disease (WD); his blood was sent for genetic study and he was started on D-penicillamine 250 mg daily. This was increased to 250 mg twice daily after 2 weeks, as he was feeling a little better and subsequently to 250 mg three times daily. His walking started deteriorating, he had more falling episodes and his memory started deteriorating further. He was brought back to the author's clinic when a MRI brain was done. His serum ammonia level (arterial blood) was 120 µg/dL (normal up to 80 µg/dL). His upper gastrointestinal endoscopy revealed presence of esophageal varices. By this time the genetic test report was available and found to be negative for WD. He was referred to a gastroenterologist for further management.

CASE 4.3

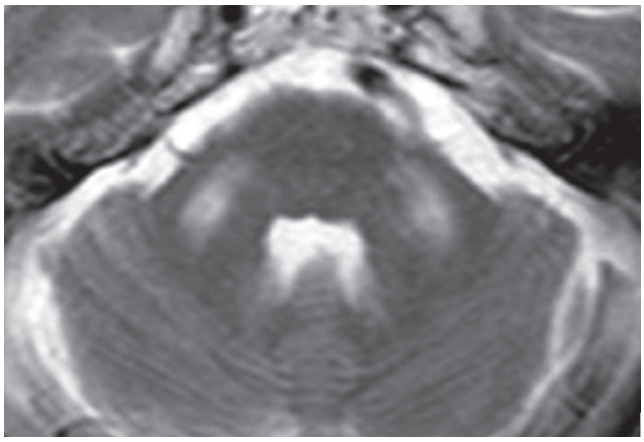
A Middle-aged Man with Alcoholic Liver Disease and Unsteadiness of Gait

Ambar Chakravarty

CASE HISTORY

A 58-year-old man with history of chronic alcoholism was diagnosed to have alcoholic cirrhosis of liver over 2 years back by a gastroenterologist. In these 2 years, he had had three hospital admissions with altered sensorium of which the last one followed an episode of upper gastrointestinal bleeding.

JAYPEE BROTHERS



(MRI: magnetic resonance imaging; T2WI: T2-weighted imaging)

FIG. 1: MRI (T2WI sequence) showing hyperintensity in both middle cerebellar peduncles in Case 4.3.

He was diagnosed to have hepatic encephalopathy (HE) on all three occasions. On one occasion he had an electroencephalography (EEG) done which showed some abnormalities. Following his last hospitalization, about 2 months back, he started developing progressive unsteadiness in walking, memory loss, and intermittently getting disoriented lasting several hours. He had no sphincteric problems. Examination revealed ill-sustained horizontal gaze-evoked nystagmus, scanned speech, postural tremor in both hands, truncal and appendicular ataxia in all four limbs, areflexia, loss of joint and position senses in legs, and mute plantar responses. A MR imaging of brain (**Fig. 1**) revealed marked cerebral cortical atrophy and cerebellar foliar atrophy with hyperintensity in middle cerebellar peduncles (MCP) (in T2WI images) as well. Electrophysiological studies revealed presence of axonopathy in all four limbs nerves.

QUESTIONS

1. **What had been the diagnosis of the presenting neurological problem in Case 4.1?**
2. **What was the underlying disorder and its various clinical forms?**
3. **Discuss briefly its pathogenesis.**
4. **Why would patients with HE need MR imaging? Discuss the genesis of cerebral edema in such patients and its management.**
5. **What was the diagnosis in Case 4.2? Briefly discuss its pathophysiology.**
6. **What does this patient's (Case 4.2) MRI show? Comment on other MR features seen in this disorder.**
7. **What are the differential diagnoses?**
8. **What had been the cause of ataxia in Case 4.3? Discuss this clinical entity.**
9. **What is the significance of triphasic waves and where else they might be encountered?**
10. **Mention briefly some nonhepatic causes of hyperammonemic encephalopathy.**

DISCUSSION

1. The elderly lady in *Case 4.1*, presented with a rather acute onset of performing a complex motor task (with the performance of which she had been very familiar), in absence of any significant motor weakness or ataxia in her hands. Additionally, she was unable to draw a rectangular box and a bisecting pentagon. Both of these problems can be grouped together under the common rubric of disorders designated as apraxias. The condition was first highlighted by the German physician Hugo Liepmann in 1900, who suggested this to result from a deficit of "motor symbolia" meaning a loss of symbolism for learned behavior. A more practical definition was suggested by Norman Geschwind (1975), who defined apraxias as "*disorders of the execution of learned movements which cannot be accounted for either by weakness, incoordination, or sensory loss, or by incomprehension of or inattention to commands.*" The so-called traditional apraxias include ideomotor apraxia, ideational apraxia, and limb-kinetic apraxias. The other group of apraxias include mostly task-specific ones such as apraxia of speech, buccolingual apraxia, constructional apraxia, dressing apraxia, oculomotor apraxia, apraxia of eye lid opening, and gait apraxia. This lady exhibited two forms of apraxias, namely ideomotor and constructional. She had no problem in ideation of how to close down the set of framed pictures; she only could not get the correct sequence of closing down. This is ideomotor apraxia. She also could not draw a box as well as a bisecting pentagon. According to the Liepmann–Geschwind model, ideomotor apraxia occurs with lesions in the Wernicke's area, arcuate fasciculus, left premotor cortex and anterior part of the corpus callosum. On the other hand, constructional apraxia is generally localizable to right posterior parietal pathologies; so also is dressing apraxias. This lady therefore appeared to have a bihemispheric disease which, based on clinical and laboratory findings, seemed to be a form of metabolic encephalopathy linked to her chronic liver disease with portal hypertension. Is apraxia a feature of HE? Davidson and Summerskill (1956) as well as Sherlock (1954), observed "*focal defects, appearing in a setting of clear consciousness, relate to disturbances in visual-spatial gnosis and are most easily elicited in the motor sphere as constructional apraxia, shown by inability to reproduce simple designs with blocks or matches. Symptoms of this defect are manifested in various difficulties. Writing is typically oblivious of*

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rulings; dressing presents problems to some patients, one cannot fill up a cheque …" A clear ideomotor apraxia, as observed in the present case had not been mentioned in the literature previously.

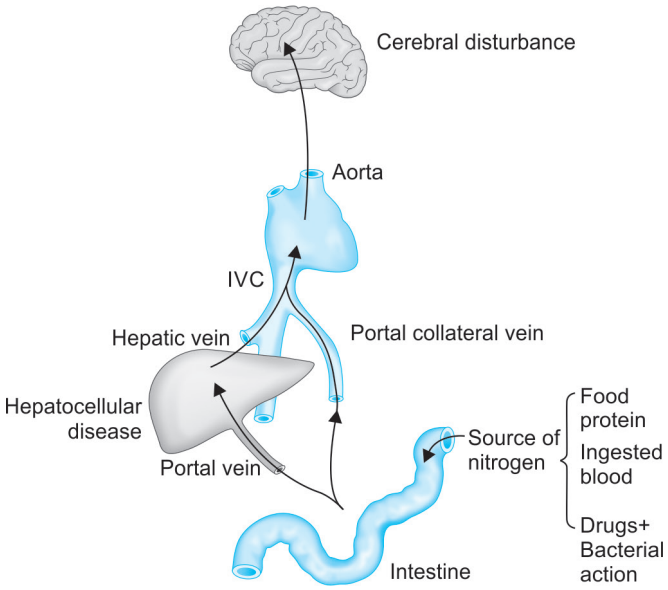
As hinted previously, the underlying disorder in this lady was undoubtedly one of HE. "*Although the Babylonians (circa 2000 BC) attributed powers of augury and divination to the liver, designating it by the term used also for 'soul' or 'mood' clinical associations between liver disease and mental disorders have been recorded since Hippocratic times. A patient with hepatitis 'developed a state-like rabies; he could not be held, said things which could not be comprehended and barked like a dog' (Morbis Internis), and the fatal illness of Hermocrates included a fluctuating delirium on the fifth day, followed by the appearance of jaundice on the sixth (Hippocrates, 460–370 BC).*"

2. Hepatic encephalopathy is currently classified into four types and these include:
   i. *Type A*: Associated with acute hepatic failure resulting from severe inflammatory and/or necrotic rapid-onset liver disease (e.g., paracetamol overdose, excessive alcohol intake or acute fatty liver caused by pregnancy or Reye's syndrome).
   ii. *Type B*: Associated with portosystemic bypass in the absence of parenchymal liver disorders and is mainly connected with congenital abnormalities.
   iii. *Type C*: Chronic hepatic disease (e.g., cirrhosis) and portal hypertension with portosystemic shunts—the most common form encountered including the present case. Subcategories include episodic, persistent (mild and severe treatment-dependent varieties), and minimal.
   iv. *Type D*: Associated with disorders of the urea cycle; rare hereditary disorders of urea biosynthesis caused by genetic defects in the urea cycle enzymes involved in synthesis of urea.

   Severity assessment: The Child–Pugh score [*also called Child–Pugh classification, the Child–Turcotte–Pugh (CTP) calculator, and the Child Criteria*] is a method to assess the prognosis and the treatment strategies to be adopted in patients with chronic liver disease, primarily cirrhosis including expected survival rate. The score is measured by five clinical score measurements of liver disease as 1–3 depending on severity. The scoring is based on total bilirubin; serum albumin; prothrombin time (PT); ascites and HE. HE can be subdivided into two types: (1) Minimal HE (MHE), and (2) Overt HE (OHE). MHE affects patients who have normal mental and neurological status; however, abnormalities appear in specific psychometric tests; OHE occurs when neurological and neuropsychiatric disruptions are overt and can be detected by simple bedside tests such as asterexis and constructional apraxia.

3. Liver cirrhosis-related neurological problems can be summarized as follows:
   - *Direct effects of cirrhosis on the nervous system*:
     - HE
     - Acquired hepatocerebral degeneration
     - Cirrhosis-related Parkinsonism
     - Cirrhotic myelopathy
     - Intracranial hemorrhage
     - Infections
     - Diffuse cerebral edema
   - *Neurologic complications specific to*:
     - *Chronic alcohol use*:
       - Osmotic demyelination syndromes
       - Wernicke encephalopathy
       - Marchiafava–Bignami disease
       - Alcohol withdrawal syndrome
       - Alcoholic cognitive decline and cerebral atrophy
       - Alcoholic cerebellar degeneration
     - Wilson's disease
     - HCV-related central nervous system (CNS) complications
4. *Concept of portosystemic shunts and encephalopathy*: A major function of the liver is to detoxify harmful protein breakdown products produced by bacterial degradation of dietary proteins or protein derived from other sources (like blood), in the gut, which are carried to the liver by the portal circulation and to release the detoxified blood in the general circulation through the hepatic veins draining into the inferior vena cava and through that to the right heart. If the liver is severely diseased (as in fulminant hepatitis and where there is acute yellow atrophy of liver due to drug toxicity), the detoxifying power is lost and hence the portal venous blood-carrying toxic substances (such as ammonia, manganese, and cytokines) would pass into the systemic circulation and then onto the brain. Alternatively, if the portal vein is blocked (thrombosed as in Budd–Chiari syndrome or blocked due to external pressure) or if there is severe rise of pressure in the portal circulation due to some intrinsic liver pathology such as cirrhosis, preexisting portosystemic connecting channels (at the gastroesophageal junction, undersurface of diaphragm, rectosigmoid junction) which under normal circumstances are closed, would open up and would drain blood-carrying toxic material from the radicles of the portal vein directly into the systemic circulation and would reach the brain parenchyma (**Fig. 2**). This pathway was postulated by Dame Sheila Sherlock back in 1954, illustrated by superb sketch in **Figure 3**.
5. The exact pathogenesis of HE is still not clear and a number of hypotheses have been suggested as depicted in **Flowchart 1**, in all of which ammonia (NH_3) seems to play a key role.

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(IVC: inferior vena cava)

FIG. 2: Pathway of portosystemic shunt and encephalopathy.
Source: Sherlock S, et al. Lancet. 1954;ii:453.



FIG. 3: Dame Sheila Sherlock (1918–2001).

- The ammonia hypothesis
- The gamma aminobutyric acid (GABA)ergic neurotransmission hypothesis
- The idea of neuroinflammation
- Oxidative and nitrosative stress
- Changes in the blood–brain barrier (BBB)
- Death of CNS cells

All the varied concepts, though apparently appear different, are in essence linked to one another (and applicable in both in cases of HE and non-Wilsonian-acquired hepatocerebral degeneration) as illustrated in the following **Flowchart 1**.

In HE, improper hepatic detoxification of ammonia (either due to liver failure or portosystemic anastomosis) expose the brain to high ammonia concentrations, and this leads to neuropsychiatric syndromes and abnormal cerebral blood flow. Ammonia is generated principally from bacterial degradation of protein in colon, degradation of glycine in small gut and also from metabolism in muscles and kidneys. In HE, the demand on muscles and the kidneys in the metabolism of ammonia attains greater significance. The low-protein diet commonly prescribed in patients with chronic liver disease, leads to loss of weight due to this enhancement of metabolic activity in muscles and may not be justified also because it leads to lesser detoxifying power of muscles.

Currently, a diet supplementation with branched-chain amino acids, is recommended as it not only reduces MHE but also improves muscle mass.

Chronic liver disease, with or without portosystemic shunting, causes failure of detoxification of NH_3 with greater NH_3 accumulation in brain. *What does NH_3 do to the brain?*

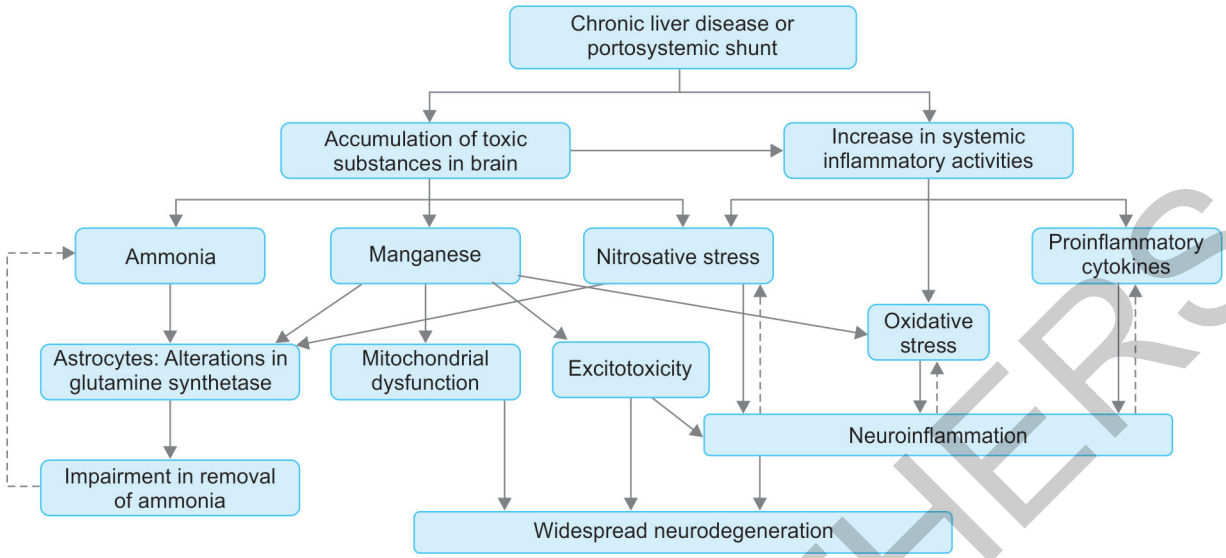
Ammonia induces astrocytic swelling as a result of osmotic imbalance. It is only the astrocytes, which can metabolize ammonia. This metabolism involves converting both glutamate and ammonia into glutamine by the enzyme glutamate synthetase. Consequently the intracellular level of glutamine rises and this being an osmocyte, imbibes water in and astrocytic swelling occurs and as a consequence, cerebral edema develops and the intracranial pressure (ICP) rises.

Increased ammonia in neural cells also produces reactive oxygen species (ROS). Further brain cell swelling occurs which modulate Zn^{++} mobilization, resulting in stimulation of the peripheral benzodiazepine receptors. By several means, hyperammonemia causes persistent neuronal depolarization and all these account for the neurobehavioral changes noted in HE and other hyperammonemic states.

Detoxification failure also results in transportation of other toxic chemicals to the brain, which include mercaptans, phenols, other benzodiazepine such as substances and products of bacterial flora. There indeed is some evidence suggesting the possible importance of acute infections due to bacterial pathogens and the resulting inflammation in the genesis of neuropsychiatric symptoms of HE.

Increased GABA-mediated neurotransmission contributes to motor function impairment and decreased consciousness in patients with HE. The exact cause of this is not known but could be related to activation of benzodiazepine receptors. Neurosteroids (such as tetrahydroprogesterone and tetrahydrodeoxycorticosterone) are potent agonists of the GABA-A

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FLOWCHART 1: Hypotheses suggesting pathogenesis of hepatic encephalopathy.

receptor, acting through a unique binding site to enhance GABAergic neurotransmission.

Hyperammonemia cannot be the sole factor generating the cascade of events leading to HE. Sepsis is most certainly an important precipitating factor.

Sepsis induces an inflammatory response which enhances the cascade of neutrophil adhesion, migration across the BBB and release of chemokines, pro-inflammatory cytokines, proteases, and ROS as well as inflammatory gene transcription. At the same time, astrocytes and microglial cells release cytokines (IL-1 and IL-6) in response to injury or inflammation. This inflammatory response would raise the question of use of anti-inflammatory agents in treatment of HE.

Oxidative and nitrosative stress are the basis of the "*two-hit hypothesis*" of HE pathophysiology. The *first hit* is the hyperammonemia of liver disease which induces the generation of ROS. The *second hit* is the occurrence of gastrointestinal bleed, which provides a further source of ammonia generation, increasing the production of ROS and more astrocytic damage.

It would not be out of place to discuss the pathogenesis of cerebral edema at this stage. The principal cause of cerebral edema in liver failure is astrocytic swelling caused by the accumulation of ammonia and glutamine inside the astrocytes as discussed earlier. In addition, a "Trojan horse" hypothesis has been suggested which proposes that glutamine itself serves as a carrier of ammonia into the mitochondria, which enhances oxidative stress and energy failure, both of which results in further astrocyte swelling, brain edema, and raised ICP. Apart from gastrointestinal bleeding and sepsis, raised ICP is an important cause of death in liver failure and HE. Clinical suspicion of brain swelling is suggested by deepening coma, irregular breathing pattern, bradycardia, inequality of pupil size and abnormal ocular movements. Confirmation is usually made on neuroimaging which reveals effacement of sulci, chink ventricles and evidence of uncal herniation with asymmetric width of perimesencephalic cistern. Gray-white distinction is also obscured. Ideally ICP monitoring is indicated.

Management principles for raised ICP in HE include:

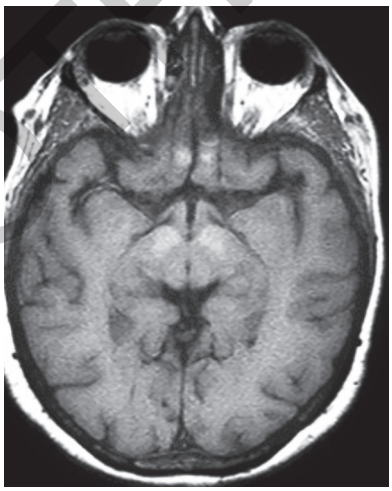
- Avoidance of Valsalva's maneuvers caused by motor agitation, cough, and suctioning.
- Facilitating venous return by correct positioning of the head (30° elevation) and neck (straight) in neutral position
- Detecting and treating aggravating conditions such as seizures, fever, hypertension, hypovolemia, hypoglycemia, and electrolyte disturbances.
- Osmotic therapy either with mannitol or hypertonic saline (target osmolarity <320 mOsm/L, target Na 145–150 mmol/L)
- Mechanical ventilation with a target $PaCO_2$ between 30 and 45 mm Hg
- Sedation with propofol or barbiturates
- Moderate hypothermia (32–34°)
- ICP monitoring with transcranial Doppler (TCD) or with extradural or subdural devices. The former is preferred because of the associated coagulopathy of liver disease.
- Surge increases in ICP can be managed with temporary hyperventilation ($PaCO_2$ 28–35 mm Hg) and /or mannitol or hypertonic saline bolus.

6. All patients with HE ideally should have neuroimaging done, preferably MR imaging. HE is not the only cause of deterioration in conscious level in patients with chronic liver disease or fulminant hepatic

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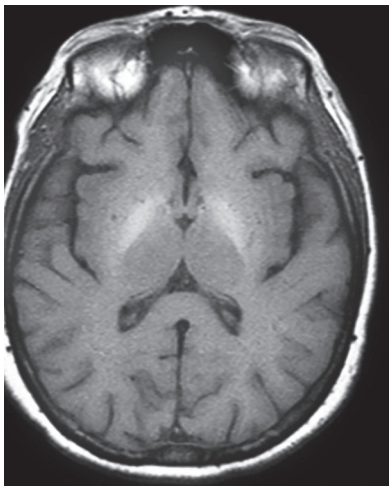
disease—infective or toxic. Intracranial bleeding needs exclusion because of the common occurrence of coagulopathy related to lowered platelet count and raised INR. Also as mentioned earlier, imaging is a reliable method of detecting cerebral edema and associated raised ICP. Rarely, Posterior Reversible Leucoencephalopathy Syndrome can also be detected in HE. Role of imaging in chronic hepatocerebral degeneration would be mentioned later in this section.

7. Clinically, HE can be episodic, chronic, or minimal. Episodic HE is characterized by rapid onset of a confusional syndrome including neuromuscular abnormalities and impaired mental state. Diagnosis is clinical and requires demonstration of persistent neurologic manifestations in a patient with severe liver failure or portosystemic shunt or both. Chronic HE may be recurrent, manifesting as frequent episodes of acute HE similar to the ones seen in episodic HE, which may be spontaneous or secondary to a precipitating factor. However, in contrast to episodic HE, patients with recurrent chronic HE demonstrate subtle neurologic abnormalities in between the acute episodes. Persistent chronic HE develops when the features cannot be reversed despite adequate treatment. Minimal HE refers to patients with cirrhosis or portosystemic shunts who have subtle abnormalities in cognitive functions that cannot be detected by standard clinical examination and manifest only while performing complex tasks.
8. In *Case 4.2,* the principal differentials include a Parkinsonian syndrome related to chronic hypertension (vascular Parkinsonism), normal sure hydrocephalus (which is very often associated with presence of chronic ischemic changes in the brain parenchyma), late-onset WD, non-Wilsonian acquired hepatocerebral degeneration (AHCD) and cirrhosis-related Parkinsonism. The associated hepatosplenomegaly, altered liver function tests (especially reversal of albumin–globulin ratio) combined with normal copper metabolism studies, would strongly favor the diagnosis of *non-Wilsonian hepatocerebral degeneration*. Cirrhosis-related Parkinsonism would remain a possibility but in that case there would have been more pronounced bradykinesia and rigidity; tremor is usually not marked. As a major feature in the pathogenesis of AHCD is manganese deposition, a remote possibility would be manganese-related neurological problems, seen mostly in miners. This would be discussed later. In the present case, absence of history of alcoholic addiction needs attention. In presence of such a history, the liver disease would likely to be alcoholic in nature. In such conditions, the differentials would include conditions, generally, associated with alcoholic liver disease such as osmotic demyelination syndromes, Marchiafava–Bignami disease, alcoholic cerebellar degeneration, and ataxia plus syndrome.
9. The pathogenesis of AHCD is different from that described in relation to acute HE. Acquired hepatocerebral degeneration results from a neurotoxic substance from the portal circulation bypassing hepatic metabolism and entering into the systemic circulation traversing the BBB. Manganese is one such potential neurotoxin that could accumulate in the mitochondria of the globus pallidus damaging the glial cells and disrupting their energy metabolism. The pathological changes observed in such cases include hyperplasia of astrocytes, necrosis with cavitory changes in the deeper layers of cortex, and the lentiform nucleus along with loss of nerve cells in the cerebral cortex, putamen, thalamus, cerebellar cortex, and dentate nuclei. The MR scan done in *Case 4.2* are given in **Figures 4** and **5**.



(MRI: magnetic resonance imaging)

FIG. 4: MRI of brain (T1) in *Case 4.2* showing hyperintensities in both crus cerebri.



(MRI: magnetic resonance imaging)

FIG. 5: MRI brain (T1) in *Case 4.2* showing hyperintensities in both globus pallidi.

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Hyperintense signals were seen symmetrically in the crus cerebri and globus pallidus in T1 and fluid-attenuated inversion recovery (FLAIR) images. At times, increased signal intensity in the dentate nuclei bilaterally on T2-weighted images (T2WI) have been noted which appear indistinguishable from those seen in WD. T1-weighted images (T1WI) hyperintensities result from manganese accumulation. Manganese being a paramagnetic material shortens the T1 relaxation time, resulting in hyperintensity on T1WI without altering signal intensity on T2WI. The concentration of manganese in the basal ganglia was found to be higher in AHCD patients than in controls. Since the clinical symptoms, neuropathological features, and MR imaging appearance of AHCD closely resemble those seen in WD, the term pseudo-Wilson disease had often been used. Apart from WD, the only other differential, considering both clinical and radiological features would be chronic manganese poisoning encountered in miners. The principal differentiating features between these three closely resembling clinical syndromes are given in **Table 1**.

Chronic manganese toxicity of the CNS had been studied by Wadia in early 1960s amongst underground mine drillers in Central India and the notable feature had been Parkinsonism with marked loss of postural balance. The other characteristic feature had been pathological laughter, "*a smile, broke into a grin, and the grin into a rising laughter and crowing, touching off a similar response in others, leading to peals of grouped laughter*." (Wadia and Wadia 2005).

10. In *Case 4.3*, a middle-aged gentleman, already diagnosed as a case of alcoholic cirrhosis of liver had had three episodes of HE, of which one episode followed gastrointestinal bleeding. Recovery occurred in all three episodes following treatment with gut sterilization, intravenous antibiotics, and mannitol. The neurological problem predominantly consisted of truncal ataxia and appendicular ataxia of all four limbs; ill-sustained gaze-evoked nystagmus, areflexia with loss of proprioceptive sensation and electrophysiologic demonstration of a peripheral neuropathy predominantly axonopathy. Additionally he had some degree of cognitive decline. Imaging revealed cerebellar volume loss along with hyperintensities in the MCP.

So, this man's ataxia seems multifactorial: Cerebellar ataxia related to cerebellar volume loss presumably from chronic alcoholism; as well as a peripheral neuropathy with sensory ataxia, again related to prolonged alcohol use. However, MCP hyperintensity (in T2WI sequence only) is not pathognomonic of AHCD alone but is also seen in olivopontocerebellar atrophy, SCA 1 and 2, Wilson's disease, acute disseminated encephalomyelitis (ADEM), HIV encephalitis, Fragile X syndrome, Huntington disease 2-like, adrenoleukodystrophy, hypoglycemia, CNS lymphoma, and other posterior

Table 1: Differentiating features between Wilson's disease (WD), acquired hepatocerebral degeneration (AHCD) and chronic manganism.

WD	AHCD	Chronic manganism
Serum ceruloplasmin ↓	Abnormal liver function tests (LFTs)	Increased manganese levels in whole blood
24-hour urinary copper ↑	Normal-to-slightly increased ammonia level	
Abnormal LFT	Increased manganese levels in whole blood and CSF may be shown	
Hemolytic anemia +		
Genetic testing: ATP7B mutations		
Imaging: • *T2-MRI*: Hyperintensities in the thalamus, lentiform and caudate nuclei, midbrain ("face of the giant panda")	Imaging: • *T1-MRI*: Hyperintensities in the globus pallidus, putamen, and substantia nigra • *T2-MRI*: MCP and cerebellum • *F-DOPA and DAT scan*: Conflicting results (normal uptake and reduced uptake of F-DOPA and DAT)	Imaging: • *T1-MRI*: Hyperintensities in the globus pallidus and substantia nigra • F-DOPA and DAT scan: Conflicting results (normal uptake and reduced uptake of F-DOPA and DAT)
Pathology: Opalski cells, Alzheimer type II astrocyte, cavitations	*Pathology*: Alzheimer type II astrocyte, polymicrocavitation, CPM/EPM	*Pathology*: Alzheimer type II astrocyte

(AHCD: acquired hepatocerebral degeneration; CPM: central pontine myelinolysis; CSF: cerebrospinal fluid; DAT: dopamine transporter imaging; EPM: extrapontine myelinolysis; F-DOPA: fluoro-3,4-dihydroxyphenylalanine; MCP: middle cerebellar peduncles; MRI: magnetic resonance imaging; WD: Wilson disease)

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fossa neoplasms. The term Ataxia Plus Syndrome has been used in relation to this case as here in addition to ataxia of cerebellar origin, the patient had peripheral neuropathy and speech and cognitive changes along with postural tremor. The speech may be scanning, staccato, or explosive. Nystagmus is uncommon and in this case though gaze evoked and horizontal, had been ill sustained. A pure cerebellar syndrome with cerebellar foliar and Purkinje cell atrophy may occur in alcohol-related liver diseases.

The T2WI hyperintensity in the MCP here is probably not related to manganese accumulation but perhaps related to altered methionine metabolism and cytokine generation.

11. This patient had had three episodes of HE. During one such episode his EEG showed presence of triphasic waves (**Fig. 6**). Triphasic waves are abnormal electroencephalographic waveforms, detectable in patients with altered sensorium which may be any form of encephalopathy or structural brain lesions. First described by Foley in 1950 in a patient with HE, as "blunted wave form," they were originally thought to be specific for HE but subsequently recorded in several other conditions with altered sensorium. The waveforms have three distinct phases: Surface positive wave of high amplitude (>70 μV), preceded by a low-amplitude negative deflection, and followed by a slow rising broad negative deflection. They may be mistaken at times for electrographic seizure discharges of nonconvulsive status epilepticus (NCSE). Suspected cases should have a benzodiazepine injection which would abolish an electrographic seizure discharge with clinically detectable improvement in level of sensorium.

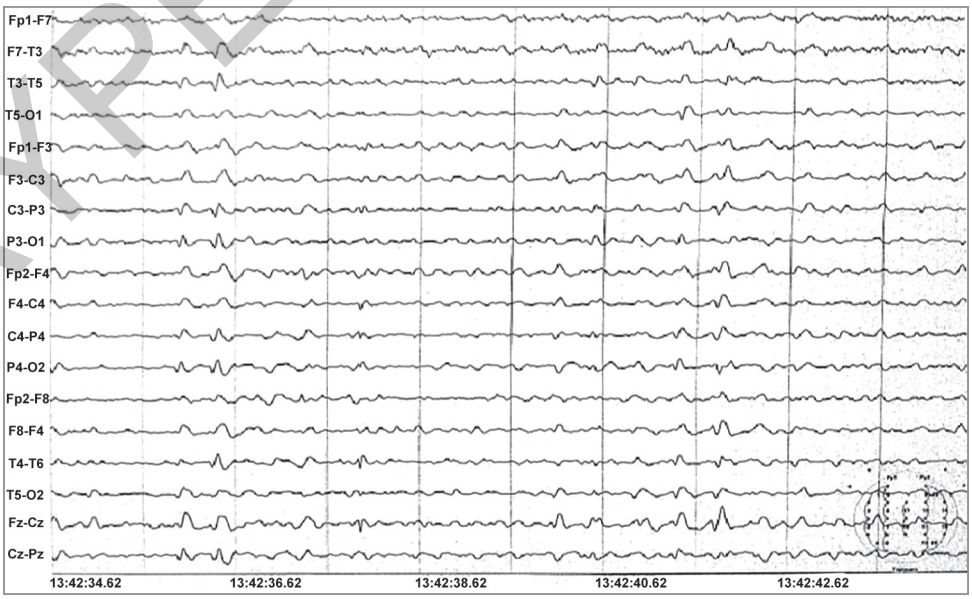
Conditions where triphasic waves are commonly recorded include: Ictal or postictal state; serotonin syndrome, Maple syrup urine disease, naproxen overdose, lithium toxicity, antibiotics such as cefepime, hyperthyroidism, hypothyroidism, HE, renal failure, hypernatremia, hyponatremia, hypercalcemia, hypoglycemia, pregabalin toxicity, and hyperosmolar state.

Structural brain lesions associated with triphasic waves include: Cerebral abscess, thalamic gliomas, craniopharyngioma, pontine stroke, cerebral carcinomatosis, multifocal cerebral lymphoma; Creutzfeldt–Jakob disease (CJD), Alzheimer and other neurodegenerative diseases, head trauma, subdural hematoma, and carcinomatous meningitis.

Triphasic waves need to be identified and differentiated from normal EEG variants and other abnormal EEG waveforms such as electrographic seizures and various types of periodic discharges. In the absence of asterexis (flap) in a patient with altered sensorium with triphasic waves in EEG, neuroimaging is warranted to exclude structural abnormalities, which can cause triphasic waveforms.

12. *Nonhepatic causes of hyperammonemia*: Around 90% of cases of hyperammonemic encephalopathies encountered in clinical practice are due to liver disease principally cirrhosis of liver. Others can be due to either increased ammonia production or diminished ammonia metabolism or ammonia excretion in the urine.

Increased ammonia production can be encountered in malignancies, especially hematological during chemotherapies as in leukemias and myelomas; infections caused by urea-producing bacteria such



(EEG: electroencephalography; HE: hepatic encephalopathy)

FIG. 6: EEG during HE in *Case 4.3* showing triphasic waves.

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as *Proteus mirabilis*, *Escherichia coli*, *Klebsiella,* and *Providencia rettgeri*; conditions with extreme protein load and metabolism (severe muscular activity) such as seizures, severe exercise, starvation, total parenteral nutrition, and gastrointestinal bleeding.

Decreased ammonia elimination may occur in organic acidurias, urea-cycle disorders, dibasic aminoaciduria, impaired fatty acid oxidation, and disturbances in pyruvate metabolism. Additionally, noncirrhotic congenital portosystemic shunts and the intake of certain drugs [e.g., valproic acid (VPA), glycine, ribavirin and carbamazepine] may induce hyperammonemic encephalopathy.

LEARNING POINTS

- Recognition of both ideomotor and task specific apraxia as early features of HE is important.
- The pathogenesis of encephalopathy associated with acute hepatic failure is different from the one which occurs as a result of portosystemic shunt commonly associated with cirrhosis of liver.
- Acquired hepatocerebral degeneration needs differentiation from WD; the former results from brain accumulation of manganese while the latter is related to copper deposition in the basal ganglia. The MRI appearances are also different.
- Diagnosis of AHCD is often missed in patients presenting with a gait disorder and cognitive decline in absence of history of alcoholism.
- Ataxia associated with alcoholic liver disease is often multifactorial in origin—alcoholic cerebellar degeneration combined with sensory ataxia related to peripheral neuropathy. Middle cerebellar peduncular hyperintensity is not specific for alcoholic liver disease.

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CASE 4.4

The Brain, Liver, and Kidney Triumvirate

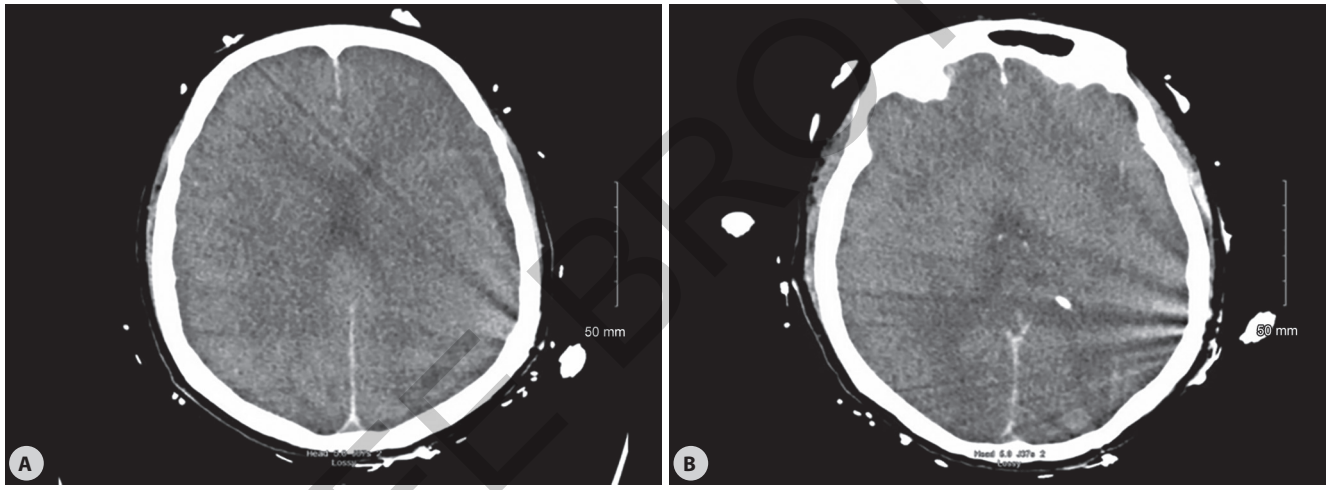
Yesica Andrea Campos, Venkatesh Ayagari

CASE HISTORY

A 50-year-old female presented to the emergency department complaining of increase in swelling on the legs and increase in abdominal girth for over a month. She had a history of hypertension and cirrhosis of unknown etiology and did not see a doctor for over a year. On admission, the patient had ascites and diffuse 3+ lower-extremity edema. On neurological examination, she was alert and fully oriented. She was able to move all four extremities against gravity without assistance and there was no evidence of asterixis. The patient displayed signs of acute renal failure [creatinine 4.1 mg/dL, blood urea nitrogen (BUN) 108 mmol/L; sodium 133 mmol/L], and coagulopathy on admission [prothrombin time (PT) 29.6, international normalized ratio (INR) 3.1, partial thromboplastin time (PTT) 49.6, hemoglobin (Hb) 6.6 g/dL, platelets 85 × 10^9/L]. Diuresis with spironolactone and furosemide was initiated. She required transfusion of multiple blood products due to severe anemia and thrombocytopenia. Two days later, the patient was found to

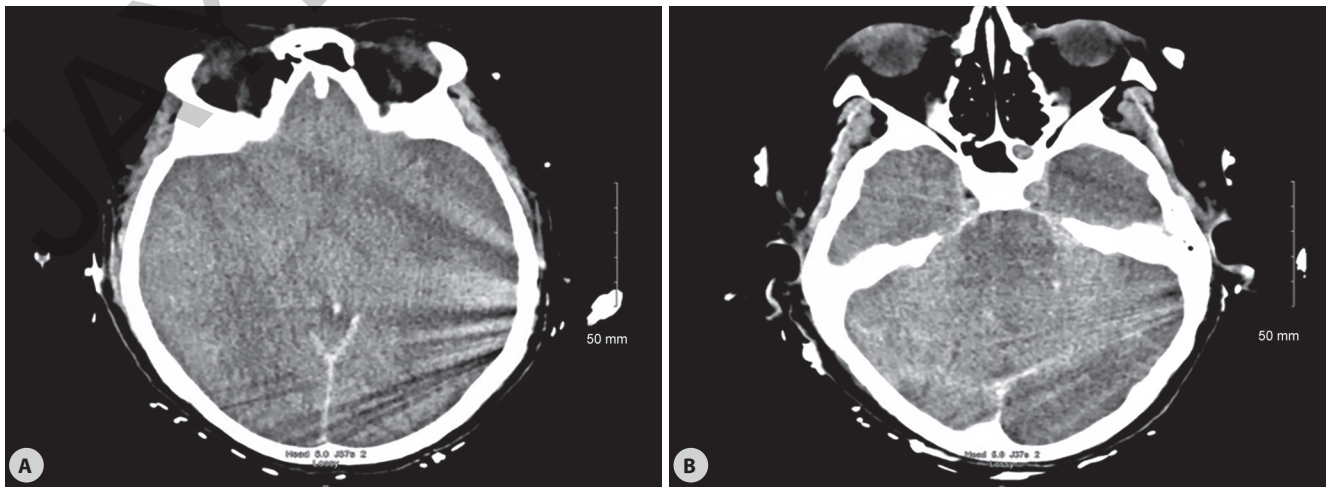
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be unresponsive to sternal rub. Pupils were 4 mm reactive bilaterally. External ocular movements were intact by Doll's eye maneuver and she had a positive corneal and cough reflex. Her computed tomography (CT) of head was unremarkable. CT angiography(CTA) of the head did not reveal a large-vessel occlusion, dissection, or aneurysm. The patient was started prophylactically on levetiracetam due to concern for seizures. However, the electroencephalogram did not reveal any seizure activity. Triphasic waves were noted. Laboratory evaluation showed evidence of hyperammonemia (232 µmol/L), severe normocytic anemia and thrombocytopenia (Hb 6.1 g/dL, platelets 34 × 10^9/L) and worsening of acute renal failure (creatinine 4.4 mg/dL, BUN 115 mmol/L) with normal sodium levels (140 mmol/L). The patient mental status continued to decline and she was intubated and mechanically ventilated. The ammonia levels started to increase up to 325 µmol/L despite management with lactulose. The patient was initiated on continuous renal replacement therapies (CRRT). The next day, she developed myoclonic jerks. Neurological examination at that time showed 3 mm bilaterally nonreactive pupils, and no corneal or gag reflex could be elicited. She had no motor response to pain. The patient was started on continuous infusion of propofol and midazolam. A CT head showed diffuse cerebral edema (**Figs. 7A** and **B**) and the patient received 30 mL of intravenous 23.4% saline followed by a continuous 3% hypertonic saline infusion for a target sodium goal of 150 mEq/L. Electroencephalographic monitoring showed diffuse low-voltage delta activity with no variability or reactivity. After CRRT, ammonia levels were eventually decreased down to 94 µmol/L, however the patient remained comatose. Pupils were nonreactive to light. She had no brain stem reflexes including corneal, gag, or cough, except for breathing. Follow-up CT (**Figs. 8A** and **B**) of the head showed



(CT: computed tomography)

FIGS. 7A AND B: Plain CT scans of brain at presentation showing effacement of sulci and chink ventricles suggestive of gross brain swelling due to cerebral edema.



FIGS. 8A AND B: Follow-up CT scans of head showing worsening of brain swelling/edema.

JAYPEE BROTHERS

worsening of diffuse cerebral edema with effacement of cortical sulci and compression of basal cisterns. She developed multiorgan dysfunction, and disseminated intravascular coagulation and expired.

QUESTIONS

1. **What are the clinical features of hepatic encephalopathy?**
2. **What are the mechanisms of cerebral edema in patients with hepatic dysfunction?**
3. **How should patients with acute and acute-on-chronic liver failure with encephalopathy be monitored? Specifically, what is the role of ICP monitoring?**
4. **What is the role of osmotic therapy in the management of cerebral edema in the setting of liver failure?**
5. **What other measures could prevent the worsening of neurological status in this patient?**
6. **What is the role of CRRT in the management of hyperammonemia?**

DISCUSSION

Hepatic encephalopathy is a neuropsychiatric syndrome caused by chronic liver disease and portosystemic shunting. It represents a major complication for acute and chronic liver failure and up to 40% of cirrhotic patients will develop HE at some point during their clinical course. The clinical spectrum of the disease includes subtle symptoms including mild lack of awareness, disoriented behavior, and coma. Some motor symptoms including asterixis, hypertonia, hyperreflexia, and positive Babinski sign can be present. More frequently, patients display signs of extrapyramidal dysfunction such as muscular rigidity, bradykinesia, hypokinesia and dyskinesia. The pupils are initially normal but may become sluggish and eventually nonreactive. Oculocephalic reflexes are usually preserved but fixed dysconjugate gaze has been reported. Limb twitching progressing to myoclonus may be seen.

Multiple studies have shown the association of HE with increased risk of death, independently of other organ failure. Experts have proposed a classification of HE into type A associated with acute liver failure, type B associated with portosystemic bypass without intrinsic liver disease, and type C associated with chronic liver disease. In general, acute liver failure is more frequently associated with cerebral edema and increased ICP.

The pathogenesis of HE is complex and not fully understood. However, one of the key mediators in the development of HE is hyperammonemia. The major supplier of plasma ammonia is colonic breakdown of ingested protein by bacteria. The main metabolism of the ammonia occurs in the periportal hepatocytes which convert it to urea which is subsequently cleared by the kidneys. When there is evidence of liver failure ammonia accumulates and is shunted unto the systemic circulation. When serum levels are elevated, ammonia crosses the cerebral brain barrier and causes neural dysfunctions which leads into HE. A rapid elevation of ammonia can lead to cerebral edema particularly on those patients with no prior liver disease. Ammonia is taken up by astrocytes where glutamine synthetase converts ammonia and glutamate into glutamine. Glutamine acts as an osmolyte and increases cerebral edema. It also enters mitochondria where it is converted to glutamate and ammonia which leads to impaired cell respiration. Other potential modulators of cerebral edema include proinflammatory cytokines such as tumor necrosis factor (TNF), aquaporin-4, and impaired cerebrovascular autoregulation leading to increased cerebral blood flow.

In general, the management is focused on preventing complications related to HE including brain herniation. Patients at particular risk for developing cerebral edema are those with rapid development of HE (e.g., acetaminophen toxicity), high-grade HE, high serum ammonia (>150–200 μmol/L), younger age, need for vasopressors or renal replacement therapy and those with sepsis or high sequential organ failure assessment (SOFA) scores. Since the most devastating complications are related to increased ICP and cerebral edema, adequate monitoring is essential. In addition to serial clinical examination, ICP monitoring should be considered. However, these patients are often at risk of bleeding complications and coagulopathy and there are no randomized controlled clinical trials that demonstrate the utility of the intraparenchymal monitors in HE. Some small case series studies have shown a modest benefit of intraparenchymal monitors in patients with grade IV HE with reasonable likelihood of survival and protocol reversal coagulopathy including administration of recombinant factor VIIa, desmopressin, with a goal platelet count > 50,000/mm^3 and fibrinogen >100 mg/dL. In this case series, only 4/37 patients died from brain herniation and uncontrolled ICP and only one developed a hematoma. However, in recent large cohorts, an ICP monitor is inserted in <15% of patients. Other surrogates of ICP such as optic nerve sheath diameter monitoring, pupillometry, and measurement of pulsatility index by TCD ultrasound have not been validated.

The general principles for management of cerebral edema include sedation with propofol, intubation, and mechanical ventilation. Procedures such as suctioning should be minimized. If an ICP monitor has been placed,

JAYPEE BROTHERS

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A Case-based Study

Key Features

- The present volume is perhaps the FIRST of its kind being published from India (and likely internationally in current times) looking at problems which lie in the interface of Neurology and Internal Medicine and discussing them in an interactive manner. Interactive way of learning is perhaps the most preferred and enjoyable way of learning (or revising) next only to bedside teaching or discussions.
- A total of over 170 authentic cases have been discussed. The pattern of interactive approach might have been a little variable from case to case, but the aim had always been to provide a "step care" approach to diagnosis and management.
- The Commentaries at the beginning of the book provide a "bird's eye view" of some selected problems lying in the interface of Medicine and Neurology.
- Contributors include renowned Neuroscientists from India and abroad.
- This book is suitable for Neurologists of all categories, Physicians, Pediatricians, and trainees in Medicine, Neurology, and Pediatrics.

Ambar Chakravarty is presently working as an Honorary Professor of Neurology and Emeritus Consultant at the Vivekananda Institute of Medical Science, Kolkata, West Bengal, India. Recipient of several awards and prizes including the Dr BC Roy National Award Fellowship of the Medical Council of India and awards from the Migraine Trust of London, Dr Chakravarty is a Fellow of The Royal Colleges of Physicians of London and Edinburg, Royal College of Physicians and Surgeons of Canada, Indian Academy of Neurology, and the Indian College of Physicians. In addition to extensive training in Clinical Neurology in India and UK, he worked as a Research Fellow at the Sunnybrook Medical Center, Toronto, Canada (1984), and obtained the Sanofi Travelling Fellowship in Pediatric Neurology to work at the Newcastle General Hospital, Newcastle upon Tyne, UK (1989). Dr Chakravarty had published extensively in national and international peer-reviewed journals, had been the Founder Editor of the Journal of The Association of Neuroscientists of Eastern India (1996–2006), an Editor-in-Chief of Frontiers in Neurology (2012–2016), written 10 monographs on Neurological Topics, and had delivered around 20 Orations so far. A recipient of Lifetime Achievement Awards from various organizations including the Madras NeuroTrust and his alma mater Medical College, Kolkata, Dr Chakravarty's research interests lie in Headaches, Epilepsy, Ataxias, Neuro-ophthalmology, Vestibular disorders, and Neuroscience and Art. He is a Past President of the Indian Academy of Neurology (2005–2006). He is an avid art lover, a collector, and an art critic.

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