The Role of Medical Case Reports in Advancing Neuropathology Research

Angelica Oviedo, MD
Associate Professor of Pathology
Director, Nervous System 2 Course
Burrell College of Osteopathic Medicine
Melbourne, FL
aoviedo@burrell.edu

Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

- Compare the similarities between a case report and a grant-funded neuropathology research paper
- Explain why a grant-funded neuropathology research laboratory investigator should publish a case report
- List at least 3 historical medical case reports that are significant for the advancement of medical knowledge
- Explain how a research journal may accept a case report

AANP

Is the manuscript different?

Case Report Publication

- **Introduction**
- **Clinical Case Presentation:**
  - Methods: Case History
  - Data: Image, DNA mutation
- **Discussion**
- **Conclusions**

Data

Grant-funded Research Publication

- **Introduction**
- Methods
- Data: Lots of data with statistics
- **Discussion**
- **Conclusions**

Data

AANP

CLINICAL HISTORY-NEED SUPER DETAILED CLINICAL HISTORY

- The clinical history is what makes your finding (image, mutation, immunohistochemistry, etc.) important and relevant to the people who will be reading your report
  - Medical student may write
  - Collaborator may write
- Keep a very detailed version of the clinical history: May be needed if you re-submit manuscript to a different journal
- Alter the length of clinical history to fit journal requirements

Why should you write a case report if you have a funded research laboratory?

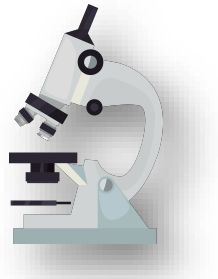
- Increase knowledge in a rare disease
- Rotating medical students:
  - Short research experiences (summer) may allow for clinical history review, reading literature, writing, submitting and publishing a case report
  - Student can learn approach to research in an abbreviated fashion
- Compare a case report to your research model
  - Does your animal model resemble human cases of the disease you are studying?
    - Yes: great
    - No: explain or explore the reasons for the differences

AANP

Other reasons to write a case report

- Teach the younger generation
  - Do you have a faculty appointment?
  - Different institutions and varying categories of faculty (clinical educator) may value medical student mentoring for promotion purposes
- Learn from the younger generation
  - Is there a different approach to what you are doing?
  - AI
- Karma

How did I end up writing case reports?
Enjoyable supplement to hospital pathology practice



- Argonne National Laboratory HS student: Summer internship, worked in lab studying rat liver carcinogenesis
- BA in Biochemistry, Northwestern University 4 years, with senior research thesis on cell biology project in Dan Linzer lab with Betsy Wilder, PhD candidate (one year, 4th author paper in Molecular Endocrinology)
- MD Northwestern University Medical School, 4 years (research environment), 2 years research in between Years 2 and 3
- NIH-HHMI research scholar National Institute of Mental Health: Basic science pharmacology project in Miles Herkenham lab (two years, first author in Brain Research)
- Pathology Residency University of Washington Medical Center: Abstracts
- Pediatric Pathology Fellowship: Director, Frank Gonzalez-Crussi encouraged me to write case reports, numerous first author papers
- Hospital practice: Wrote numerous first author case reports
- Burrell College of Osteopathic Medicine: Joey Benoit (former research dean), very helpful with strategic decisions about manuscripts and journals

AANP

What is a Case Report?

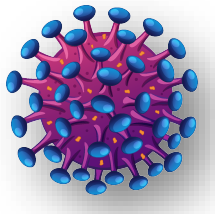
- 1-3 similar cases
- Highlight one aspect of clinical medicine: presentation, radiology, laboratory medicine, pathogenic DNA mutations and/or anatomic pathology
- IRB: Generally, exempt from full review
  - Different institutions have different rules
  - Need to check with your IRB and get exemption letter or email
  - Do not always need consent if the case is educational and there is no identifying information in the manuscript: Follow your own institutional guidelines
  - Some hospitals or journals do require consent from the family or patient
- General advice: Inform your department chair that you are working on the case report (do not include patient name in communications)

AANP

Adobe Photostock, 2023

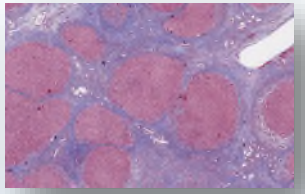
Clinical colleagues, Nursing staff, Genetic counsellors

- Consent:
  - Is family/patient returning to clinic for follow-up?
  - Select colleague that can help you if there is a language difference
  - Many families want to contribute to research and are willing to sign consent
- More history



Famous Case Reports

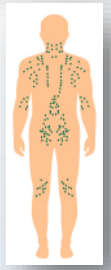
- AIDS
- Helicobacter pylori
- Regression of hepatic cirrhosis

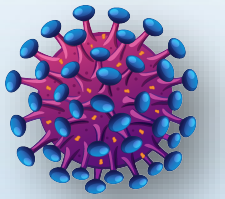


Oviedo, Pathpresenter, Cirrhosis, 2023

Adobe Photostock, 2023

AIDS Research in North America and Europe
Live version (later retroactive studies done in many countries)





- Who first identified the disease that causes AIDS? People exposed to these patients in their work that recognized something unusual.
  - 1980's: Various reports of patients with Kaposi's sarcoma and *Pneumocystis* pneumonia
  - April 1981: Sandy Ford identified unusual clusters of gay patients in New York and California with Kaposi's sarcoma and *Pneumocystis* pneumonia and alerted her supervisors and wrote a memo. She was a drug technician for the CDC in Atlanta who noticed increase in requests for pentamidine (used to treat *Pneumocystis* pneumonia)
  - There are multiple "firsts" in identification of AIDS: New York, Los Angeles, Lymphadenopathy described as common finding in patients with AIDS
  - Morbidity and Mortality Report, CDC, June 5, 1981: Described 5 gay patients with *Pneumocystis* pneumonia in Los Angeles
- Who first identified HIV, the virus that causes AIDS? Lots of basic science research on patients with AIDS
  - 1983: Luc Montagnier and Franciose Barre-Sinoussi isolated a T-cell tropic retrovirus from the lymph node of a 33-year-old French gay man, Nobel prize 2008
  - 1984: Robert Gallo NCI, isolated HIV from 48 patients and connected it with AIDS (used a control group of 115 without AIDS risk factors)
  - 1984: Levy, UCSF, isolated HIV virus and HIV antibodies in AIDS patients: Antibodies absolutely critical for identifying patients with HIV/AIDS and developing clinically useful test for exposure to virus

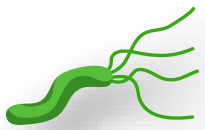
Shilts, And the Band Played On, 1987
Schmid, Nat Comm, Dec 2018
Barre-Sinouszi, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immunodeficiency syndrome (AIDS). Science 220, 868-871, 1983.

Wikepedia. Sandy Ford.
https://en.wikipedia.org/wiki/Sandy_Ford
Accessed 09 18 2023

Oviedo, M., Personal Communication (Lymphadenopathy), 1994

Abrams, AIDS-related Conditions, Clinics in Immunology and Allergy, 6:3, October 1986

AANP



Gastroduodenal Ulcers
Helicobacter pylori Gastritis and Duodenal Ulcers

- Prior to discovery/description of *H Pylori* as etiologic agent of gastric ulcers, they were thought to be caused by stress
- Ambulatory patients with gastric ulcers were told they needed to learn to manage their stress
- (Where did this incorrect thinking come from? ICU ulcers were well described in clinical medicine but generally occur in patients with ICU level stress)
- 1985: Robin Warren and Barry Marshall identified *Helicobacter pylori* (*Campylobacter pylori* back then) as causative of gastroduodenal ulcers
  - Warren was a pathologist: He described Campylobacter bacteria on gastric biopsies from patients with ulcers, also eventually developed breath test for *H Pylori*
  - Marshall was an internist that worked with Warren to develop the idea that bacteria can cause gastritis: He drank a broth that contained *H Pylori*, developed gastritis then took antibiotics
- Nobel prize 2005
- Ulcers caused by *H Pylori* now treated with antibiotics
- Note: This is not technically a "case report" but I included it because it is 2 clinicians that recognized something in certain patients and were able to make a conclusion based on clinical information

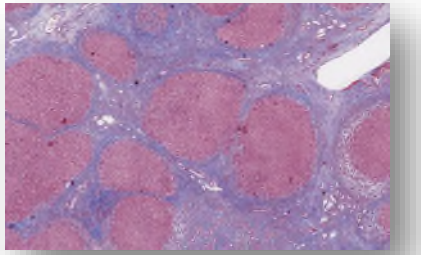
Marshall BJ, McGechie DB, Rogers PA, Glancy RJ. Pyloric Campylobacter infection and gastroduodenal disease. Med J Aust. 1985 Apr 15;142(8):439-44.
doi: 10.5694/j.1326-5377.1985.tb113444.x. PMID: 3982346.

Wikipedia, Barry Marshall
https://en.wikipedia.org/wiki/Barry_Marshall
Accessed 09 19 2023

Wikipedia, Robin Warren
https://en.wikipedia.org/wiki/Robin_Warren
Accessed 09 19 2023

AANP

Regression of Hepatic Cirrhosis



- Ian Wanless, a pathologist from Canada
- Noticed that a liver biopsy from a patient with Hepatitis B showed improvement in cirrhosis after patient received anti-viral medication
- Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. Arch Pathol Lab Med. 2000 Nov;124(11):1599-607. doi: 10.5858/2000-124-1599-ROHC. PMID: 11079009.

Personal Case Reports

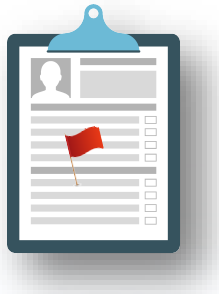
- MECP2: Severe Congenital Encephalopathy in a Male Infant (Male Rett Syndrome)
- UNC13A pathogenic mutation in an infant
  - Whole exome sequencing identified mutation but labelled it as VUS (Variant of Uncertain Significance) and not likely causative of disease
  - Phenotype of infant closely matched severe synaptic dysfunction
- NGLY1 pathogenic mutation in a 5-year-old male
- COVID19 infection of placenta
- Lots of others:
  - Many are related to a pathogenic gene mutation correlation with phenotype
  - Also, rare tumors

AANP

First Case in Practice: Severe Congenital Encephalopathy in a Male Toddler

- Severe clinical phenotype: 15-month-old male with global developmental delay and seizures
- Autopsy: Normal appearing toddler, normal brain
- The combination of a severe phenotype with a normal appearance is highly suggestive of a single gene mutation (larger pieces of chromosome duplication or deletion will usually have abnormal facies and additional malformations)
- Early 2000's:
  - Microarray was normal
  - Gene testing only done by single gene sequencing upon request
- Thorough gross and microscopic examination largely normal (small brain):
  - Not diagnostic of any known entity
  - Cause of death cardiorespiratory failure

Severe Congenital Encephalopathy in a Male Toddler -Continued



- Reviewed about 3 feet of medical chart (in the middle of changing to electronic medical record):
  - Multiple hospital admissions
  - Variable respiratory rate
- Clinical conferences: Pediatric Neurology, ICU staff, Medical Geneticists, etc.
- Unable to make a definitive diagnosis (Yes, we knew it was genetic)
- A few months later:
  - Book on Rett: Rare males with Rett (identified by female siblings) had variable respiratory rate
  - Rett syndrome generally prenatally lethal in males
- Requested MECP2 sequencing: Small deletion at intron 3/exon4 splice junction with frame shift and premature termination codon

AANP

Adobe Photostock, 2023

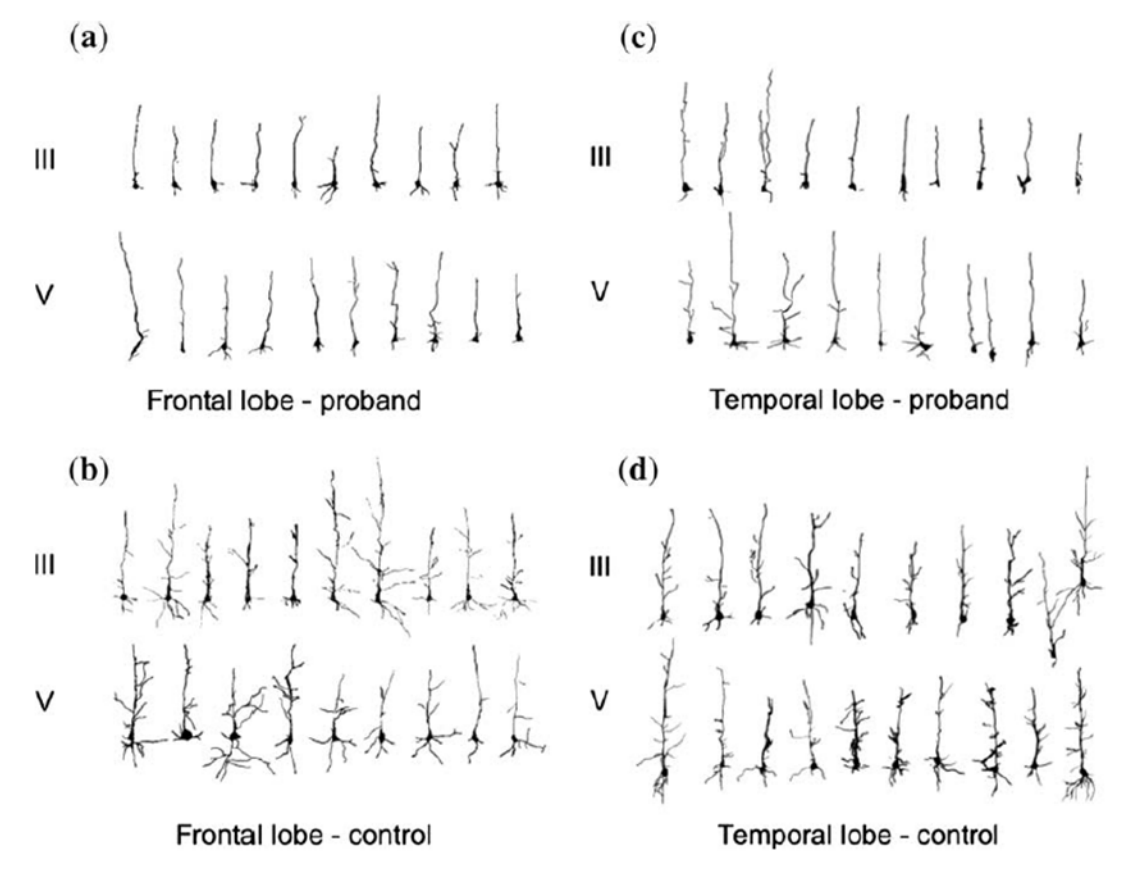
Bay Area Medical Genetics Conference
MECP2 Collaboration

- Ute Francke: Worked on mouse model of Rett syndrome at Stanford
- Did extensive detailed molecular and cell biology studies on patient fibroblasts
- Conclusion: MECP2 deletion mouse mimicked male Rett (Severe Congenital Encephalopathy) and not female Rett syndrome (Normal development followed by deterioration)
- Schüle, B., Armstrong, D., Vogel, H., Oviedo, A. and Francke, U. (2008), Severe congenital encephalopathy caused by MECP2 null mutations in males: central hypoxia and reduced neuronal dendritic structure. Clinical Genetics, 74: 116-126. https://doi.org/10.1111/j.1399-0004.2008.01005.x

AANP

MECP2 mutation in a male toddler
Markedly decreased dendritic branching

This is what data looks like in a case report



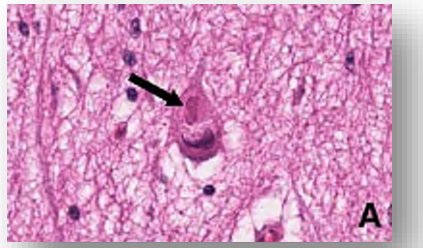
Schüle, B., Armstrong, D., Vogel, H., Oviedo, A. and Francke, U. (2008), Severe congenital encephalopathy caused by MECP2 null mutations in males: central hypoxia and reduced neuronal dendritic structure. Clinical Genetics, 74: 116-126. https://doi.org/10.1111/j.1399-0004.2008.01005.x

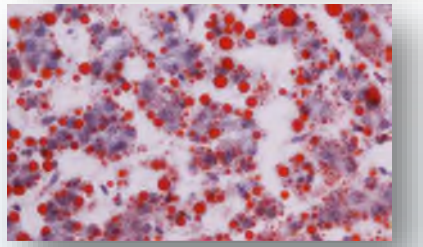
AANP

Next Case: 5-year-old male with neurodegenerative phenotype died of disease
9-month-old female sibling died of SUDI (sudden unexpected death in infancy)
NGLY1 mutation

- Autopsy
  - Boy with numerous abnormalities of liver and brain
  - Girl with non-specific findings
- 2014: Multi-author publication showing mutations in NGLY1 cause inherited disorder of endoplasmic reticulum degradation pathways
- Greg Enns, Stanford
- Enns GM, Shashi V, Bainbridge M, Gambello MJ, Zahir FR, Bast T, Crimian R, Schoch K, Platt J, Cox R, Bernstein JA, Scavina M, Walter RS, Bibb A, Jones M, Hegde M, Graham BH, Need AC, Oviedo A, Schaaf CP, Boyle S, Butte AJ, Chen R, Chen R, Clark MJ, Haraksingh R; FORGE Canada Consortium; Cowan TM, He P, Langlois S, Zoghbi HY, Snyder M, Gibbs RA, Freeze HH, Goldstein DB. Mutations in NGLY1 cause an inherited disorder of the endoplasmic reticulum-associated degradation pathway. Genet Med. 2014 Oct;16(10):751-8. doi: 10.1038/gim.2014.22. Epub 2014 Mar 20. Erratum in: Genet Med. 2014 Jul;16(7):568. Chen, Rui [added]. PMID: 24651605; PMCID: PMC4243708.
- No pathology shown in this multi-author paper: Paper focused on mutations and clinical phenotypes

2014 NGLY1 Enns paper





- Whole-genome, Whole-exome and Sanger sequencing
- NGLY1 loss of function results in severe phenotype
- 8 patients
- Detailed clinical phenotype-mutation correlation
- So, how did we get another paper from these patients?
  - Original paper did not have autopsy findings
  - We submitted a manuscript with detailed neuropathologic findings
- Stuut T, Popescu O, Oviedo A. N-Glycanase 1 Deficiency Is a Rare Cause of Pediatric Neurodegeneration With Neuronal Inclusions and Liver Steatosis. Cureus. 2021 Oct 29;13(10):e19126. doi: 10.7759/cureus.19126. PMID: 34858763; PMCID: PMC8614178.

AANP

Next Case:
Congenital Encephalopathy in a Female Infant

- Term gestation: Cesarean section for decreased fetal movements
- Good Apgars but poor feeding, so transferred to NICU
- Mildly dysmorphic features
- Fed through gastrojejunostomy tube
- Died at 8 months
- Autopsy brain findings:
  - Vertically oriented hippocampi
  - Absent sub-cortical U-fibers
  - Atrophic brain and spinal cord

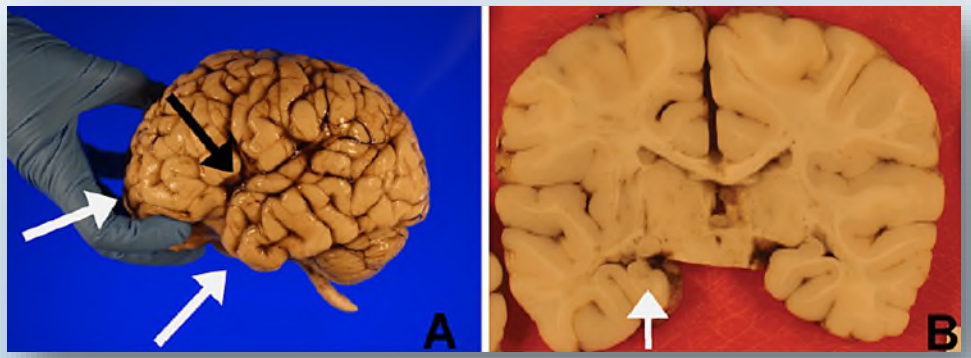
Congenital Encephalopathy in a Female Infant

- Exome sequencing (only sequence protein coding regions): Homozygous UNC13A nonsense variant
- Initial interpretation by sequencing laboratory was that this mutation was not pathogenic because UNC13A mutation had not been previously reported as disease-causing
- Autopsy findings very unusual and correlate with single gene mutation phenotype
- One previous report on muscle biopsy with UNC13A mutation: Phenotype very similar to our case
- UNC13A: Protein involved in docking and fusion of synaptic vesicles and central neuronal synapses and neuromuscular synapse
- Note: Knock-out animal models of UNC13 related proteins have similar phenotype
- Conclusion: UNC13A mutation is disease-causing in this infant

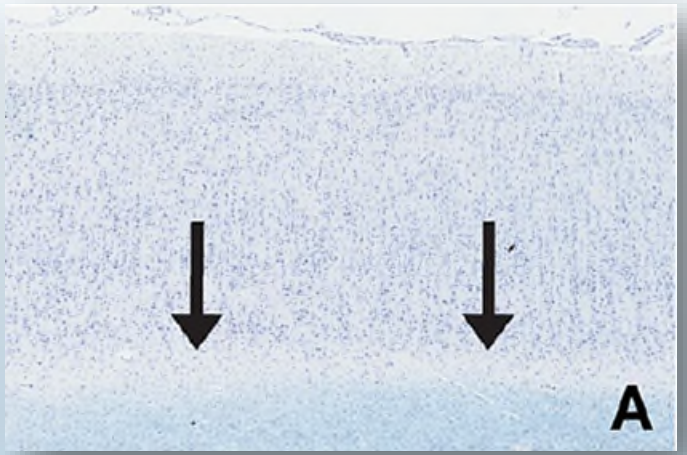
AANP

UNC13A Mutation
Congenital Encephalopathy in a Female Infant

- Mullins JR, McFadden K, Snow N, Oviedo A. Homozygous UNC13A Variant in an Infant With Congenital Encephalopathy and Severe Neuromuscular Phenotype: A Case Report With Detailed Central Nervous System Neuropathologic Findings. Cureus. 2022 Oct 27;14(10):e30774. doi: 10.7759/cureus.30774. PMID: 36447687; PMCID: PMC9701132.



This is what data looks like in a case report



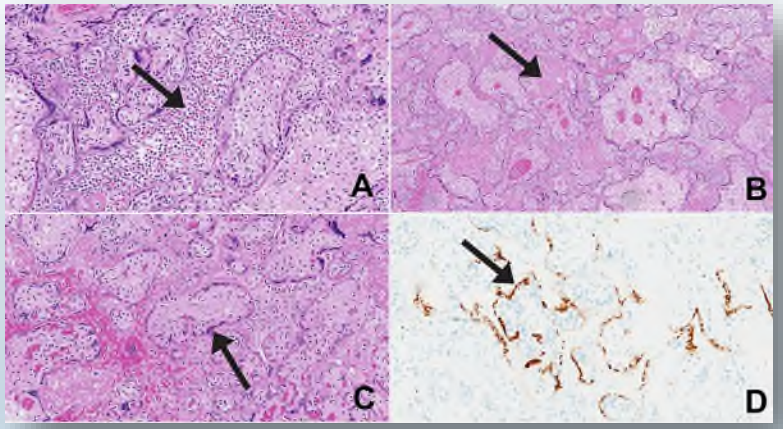
LFB: Loss of sub-cortical U-fibers

AANP

Last Case: COVID19 Pandemic

How does COVID19 affect fetus with maternal infection during pregnancy?

- Being in the right place at the right time and knowing a lot about placentas
- Collaborative report on mechanism of disease for COVID19 placental infection
- Bewley DJ, Lee J, Popescu O, Oviedo A. SARS-CoV-2 Placental Infection in an Unvaccinated Mother Resulting in Fetal Demise. Cureus 13(12): e20833, 2021. doi:10.7759/cureus.20833
- Schwartz DA . . . Oviedo et al. Placental Tissue Destruction and Insufficiency from COVID-19 Causes Stillbirth and Neonatal Death from Hypoxic-Ischemic Injury: A Study of 68 Cases with SARS-CoV-2 Placentitis from 12 Countries. Arch Pathol Lab Med. 2022 Feb 10. doi: 10.5858/arpa.2022-0029-SA.



COVID-19 infected placenta with positive RNA in situ hybridization

AANP

So where do you find a good case report to write? Observe your environment

  - Rare tumors, autopsies
  - Is there something unusual about patient age, presentation, genetics?
- Patient care conferences:
  - Tumor board:
    - Rare tumors
    - Unusual mutation: In tumor or in patient
    - Unusual location
    - Unusual presentation
  - Gastrointestinal Clinical Conference
  - Radiology Clinical Conference
  - Endless numbers of clinical conferences have a concentrated number of unusual or rare patients

Where do you submit your case report?

- Some journals have “Case Report” categories of submission
- Generally limited numbers of authors and references
  - If you exceed limits, there may be a fee (e.g., Cureus)
- Specialty journals:
  - American College of Gastroenterology Case Reports: Giant Cell Hepatitis in an adult (Burrell medical student, Miranda Martinez-Moad)
  - Pediatric Neurology: Occludin mutation neuropathology

J of Neuropathology and Experimental Neurology (JNEN)
Dr Jack Lee (editor), email communication June 11, 2024

- Author does not need to have a previously published research paper

Letters to the Editor :

Brief manuscripts, (e.g. a report of a single novel or unique case), should be submitted as a Letter to Editor with an upper limit of five double-spaced text pages. The letter should not include distinct sections such as an Abstract, Introduction, Materials and Methods, Results or Discussion. Figures, tables, and references (up to 15), if included, must fit within these constraints. A maximum of either two figures or one figure and one table may be included. Supplementary data files should not be included. Only reports deemed to be of high scientific value and potential widespread interest to the JNEN readership will be considered for publication. Letters may also be submitted to comment on articles published in the Journal or on specific aspects of neuropathology following these guidelines

AANP

https://www.neuropath.org/jnen

Acta Neuropathologica

Case Reports

Reports on single cases may be published provided they include new pathologic, pathogenetic or clinico-pathological information. Usually, they should be submitted in the format of a letter (see below). However, Case Reports without length restrictions are occasionally published. They are restricted to exceptionally interesting, excellently illustrated single cases that provide new scientific insight.

Letters (Correspondence)

Letters may include commentaries about previous papers in Acta Neuropathologica, on other matters of interest, reports on single cases, or negative findings. Letters do not have an Abstract, nor do they have sections such as Introduction, Materials & Methods, Results and Discussion.

The title of the letter should include the message, i.e. the new finding that makes it worth publishing. Letters must not exceed 1,000 words and 2 printed pages, including figures, tables (if any) and references. One printed text page corresponds to about 800 words.

https://link.springer.com/journal/401/submission-guidelines?IFA#Instructions%20for%20Authors_Types%20of%20papers

Accessed June 11, 2024

AANP

Brain

Preliminary reports of work in progress or single case studies are not considered. More detailed studies of single cases may - in rare instances - be considered as a Report (see below) only when they resolve definitively an important problem in the field or when the data lead to a significant conceptual advance. Studies of single cases that can be readily performed on groups of patients will not be considered.

Reports

Word limit*: 2500

Abstract word limit: 200

References: 30

Display items: 4

Reports are shorter articles that describe important advances. Presubmission enquiries about reports will not be considered.

https://academic.oup.com/brain/pages/General_Instructions

Accessed June 11, 2024

Cureus

- Has “Case Report” category of submission
- Has reference number limits and author limits: If you exceed limits, there is a charge
- I have published numerous case reports in Cureus
- Founder of Cureus is a neurosurgeon, Dr John Adler

https://www.cureus.com/

Unclear on guidelines for case report submission?

- Email the editor with information about your case and ask for guidance
- Guidance:
  - Type of submission (Case, Letter, etc.)
  - Number of authors
  - Word count
  - Reference count
- If answer is no, move on, there are a lot of journals

How do I convince editors and reviewers that this case report needs to be published?

- If there is already a description of this disease:
  - I am submitting a "detailed" description of some aspect of the case
  - Example: NGLY1 mutation neuropathology case with images (previous papers described pathology with words and no images)
  - Many mutation papers describe sequencing in the setting of a clinical phenotype: Is there radiology, neurophysiology, pathology?
- Need to describe disease to a group of clinicians using a different journal type
  - If literature is heavily based in radiology, then describe need to publish in pediatric neurology literature
  - Example: Occludin mutation case submitted to Pediatric Neurology (previous papers in scientific literature)
- Unusual aspect of clinical presentation
  - Example: Congenital pulmonary airway malformation seen on CT scan for the first time in a 62-year-old female with a history of breast cancer

AANP

You submitted your manuscript, now what?

- Peer-review from journals can be very valuable:
  - If you do what the journal asks and re-submit, you will probably get accepted
  - If you cannot do what they ask, explain why and re-submit
  - Another option: Re-evaluate your thinking and re-submit. Maybe image is not beautiful enough or you need detailed molecular data
- Rejection from journal:
  - Think about their feedback very carefully
  - Discuss with your collaborators and advisers
  - Try another journal
  - Medical students: Submit to a meeting and do a platform presentation or poster
- Be strategic about timing for a meeting submission: Some journals will not accept a manuscript that has been presented at a meeting

AANP

Other avenues for publication (Not really case reports)

- Editorials/Opinion papers (I have published two of this style manuscript):
  - Most major journals will consider this category of manuscript
  - Some scientific journals will only accept this category of manuscript from author that has previously published a manuscript in their journal
- Educational papers (I myself have not published these types of papers):
  - *Academic Pathology* has "Educational Cases" category of manuscripts
  - These are fictional cases that demonstrate pathology for educational purposes

AI

- If you use AI in case preparation, should mention it in manuscript
- Check journal for guidelines
- Example in Methods:
  - *Elicit: The AI Research Assistant* was prompted using the following phrases: ‘the effects of medication during pregnancy and its effects on fetus,’ ‘antidepressant fetal withdrawal syndrome,’ ‘maternal medications and their effect on fetal development,’ ‘maternal use of SSRIs on fetal development’

Thank you

- Patients and their families
- Many clinical colleagues I’ve worked with
- Many basic science researchers I’ve worked with
- Librarians: Burrell library databases
- Pubmed
- OMIM

References

1. Barre-Sinouszi, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immunodeficiency syndrome (AIDS). Science 220, 868-871, 1983.

2. Marshall BJ, McGechie DB, Rogers PA, Glancy RJ. Pyloric Campylobacter infection and gastroduodenal disease. Med J Aust. 1985 Apr 15;142(8):439-44. doi: 10.5694/j.1326-5377.1985.tb113444.x. PMID: 3982346.

3. Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. Arch Pathol Lab Med. 2000 Nov;124(11):1599-607. doi: 10.5858/2000-124-1599-ROHC. PMID: 11079009.

AANP

Q&A