Megalencephaly-Capillary Malformation Polymicrogyria (M-CAP): A Case Study

Ashlee R. Loughan, Ph.D.
Clinical Neuropsychologist
Assistant Professor of Neurology
Virginia Commonwealth University
Massey Cancer Center

Objectives

• M-CAP
  – Diagnostic Criteria
  – Identifiable Characteristics
  – Literature
  – Treatment
• Case Study
  – Demographics
  – History
  – Evaluation Results
  – Recommendations

Demographics

• Rare syndrome first described in 1997
  – Multiple name changes given defining characteristics (M-CMTC, M-CM, M-CAP)
  – In 2012, Genetic mutation identified in gene PIK3CA
    – Mutation is thought to always occur after cell division begins - de novo mutation
• Website Registry = 181 cases
• Literature Reports = 150 cases
• Across genders
• Across ethnicities

<table>
<thead>
<tr>
<th>Age</th>
<th># Registered</th>
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<tbody>
<tr>
<td>0-2 yrs</td>
<td>32</td>
</tr>
<tr>
<td>2-10 yrs</td>
<td>100</td>
</tr>
<tr>
<td>11-18 yrs</td>
<td>37</td>
</tr>
<tr>
<td>18+ yrs</td>
<td>12</td>
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Diagnostic Criteria

<table>
<thead>
<tr>
<th>Major Criteria (requires 3)</th>
<th>Minor Criteria (requires 2)</th>
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<tbody>
<tr>
<td>Macrocephaly *</td>
<td>Midline facial capillary malformation</td>
</tr>
<tr>
<td>Capillary malformation(s) *</td>
<td>Neonatal hypotonia</td>
</tr>
<tr>
<td>Overgrowth/asymmetry *</td>
<td>Syndactyly/polydactyly *</td>
</tr>
<tr>
<td>Neuroimaging alterations:</td>
<td>Connective tissue abnormalities</td>
</tr>
<tr>
<td>Ventriculomegaly *</td>
<td></td>
</tr>
<tr>
<td>Cavum septum pellicum or</td>
<td></td>
</tr>
<tr>
<td>Cavum septum vergae</td>
<td></td>
</tr>
<tr>
<td>Cerebellar tonsillar herniation</td>
<td></td>
</tr>
<tr>
<td>Cerebral and/or cerebellar asymmetry *</td>
<td></td>
</tr>
</tbody>
</table>

Martinez-Glez et al. were able to diagnose 94% of 136 previously reported cases using their criteria.
Identifiable Characteristics

- Macrocephaly
  - [Link](http://undiagnosed.org.uk/archives/tag/macrocephaly)
  - [Link](http://www.m-cm.net)
- Capillary Malformation(s)
  - [Link](http://www.saintluc.be/en/services/vascular-anomalies)
- Overgrowth / Asymmetry
  - [Link](https://www.edmcasereports.com)
  - [Link](http://www.m-cm.net)
- Neonatal Hypotonia
  - [Link](http://autism.wikia.com/wiki/Hypotonia)
- Syndactyly / Polydactyly
  - [Link](https://www.m-cm.net)
  - [Link](http://www.wikipedia.org)

Literature

- Limited cognitive / neuropsychological data
- Most studies suggest developmental delays ranging from mild to moderate impairment
- For example: Mirzaa et al. (2012) examined 21 MCAP children

![Chart showing developmental delays and percentages]

- 100% Developmental Delay
- 38% Profound Language Delay, n = 8
- 28% Autistic Symptoms, n = 6
- 5% ADHD, n = 1
- 5% ADHD / OCD, n = 1
- 5% Normal Intelligence, n = 1

Literature Cont...

- Important Note:
  - To date, MCAP does not appear to be a condition associated with regression or decline in a person's cognitive functioning, unless an exacerbation of neuropathological processes occurs.
  - Children with MCAP are expected to make slow progress developmentally.
  - However, most children with this disorder continue to be consistently behind their peers in both academic and functional abilities.

**CHALLENGE**

This diverse presentation proves to be an obstacle when trying to identify cognitive or behavioral patterns in MCAP.

CASE STUDY

- Frances “Franny” Brown
- Diagnosed with M-CAP at age 4 months
- Referral
  - Global delays
  - Reported inattention
  - Recent academic deficits / regression

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>7</td>
</tr>
<tr>
<td>Education</td>
<td>1st grade public education</td>
</tr>
<tr>
<td>Handedness</td>
<td>Right</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>Upper Middle Class</td>
</tr>
<tr>
<td>Parental Education</td>
<td>Bachelors Degree</td>
</tr>
</tbody>
</table>

Developmental History

- Prenatal history uncomplicated
- Upon delivery, presented with
  - Cutis marmorata
  - Port wine stains
  - Large head (99th percentile – then “off the chart”) Feet malformations
- Genetic testing - none
- All developmental milestones delayed
- Continued motor deficits

Currently, there is no cure for M-CAP

Treatment varies depending on a multitude of factors including the presence and severity of specific impairments
Medical History

- Macrocephaly **
- Hemihyperplasia **
- Capillary malformations **
- Headaches
- Hydrocephalus *
- Partial complex seizures (age 2 ½)
- Syndactyly / polydactyly *
- Muscle spasms
- Bladder incontinence
- Chronic ear infections
  - Conducted hearing impairment
  - Currently wears hearing aids in both ears
- Surgery History (to date):
  - Ventriculoperitoneal shunt
  - Fourth ventricle shunt
  - Tonsillectomy
  - Adenoidectomy
  - Spinal fenestration of an arachnoid cyst
  - Chiari decompressions (3)
  - Spinal shunt
  - (1 revision)
- Medications
  - Keppra, Trileptal, prevacid

Medical History

- Neuroimaging (MRI) Findings:
  - Brain asymmetry / left hemimegalencephaly
  - Hydrocephalus (shunt placements)
  - Chiari malformations
  - Distortion of cerebellar hemisphere
  - White matter signal hyperintensities

Previous Evaluation

2012

![WJ-III Test Results](image)

Intelligence / Achievement / Memory

<table>
<thead>
<tr>
<th>Test</th>
<th>Standard Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC-IV</td>
<td>73 76 90 82 89</td>
</tr>
<tr>
<td>WIAT-III</td>
<td>69 70 55 60 60 65</td>
</tr>
<tr>
<td>LEITER-R</td>
<td>51 76 109 110</td>
</tr>
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</table>

Test Results: Adaptive Functioning

<table>
<thead>
<tr>
<th>Domain</th>
<th>Age Equivalent</th>
</tr>
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<tbody>
<tr>
<td>Communication</td>
<td>1:10</td>
</tr>
<tr>
<td>Receptive</td>
<td>2.6</td>
</tr>
<tr>
<td>Expressive</td>
<td>3.1</td>
</tr>
<tr>
<td>Daily Living</td>
<td>2.9</td>
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<tr>
<td>Personal</td>
<td>2.5</td>
</tr>
<tr>
<td>Domestic</td>
<td>3.7</td>
</tr>
<tr>
<td>Community</td>
<td></td>
</tr>
<tr>
<td>Socialization</td>
<td>2.3</td>
</tr>
<tr>
<td>Interpersonal</td>
<td></td>
</tr>
<tr>
<td>Play and Leisure</td>
<td>2.11</td>
</tr>
<tr>
<td>Coping</td>
<td>2.11</td>
</tr>
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</table>

Test Results: Executive Functioning

<table>
<thead>
<tr>
<th>Domain</th>
<th>T Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>in-role</td>
<td>68 61 69 70</td>
</tr>
<tr>
<td>Emotional Control</td>
<td>68 69 70</td>
</tr>
<tr>
<td>Initiative</td>
<td>64 65 66</td>
</tr>
<tr>
<td>Working Memory</td>
<td>73 73 73</td>
</tr>
<tr>
<td>Plan / Organize</td>
<td>65 64</td>
</tr>
<tr>
<td>Org of Materials</td>
<td>69 66</td>
</tr>
<tr>
<td>Monitor</td>
<td></td>
</tr>
</tbody>
</table>

![Behavior Rating Inventory of Executive Function](image)
Test Results: Behavior and Emotional Screening

Behavior Assessment System for Children – 2nd Edition

Questions and Discussion

Contact Information:
Ashlee R. Loughan, Ph.D., M.Ed.
Virginia Commonwealth University
Massey Cancer Center
Richmond, VA
804-828-9815
ashlee.loughan@vcuhealth.org

Interpretation / Take Home

- Consistent with MCAP literature, Franny presented with multiple neurologic complications which should raise concerns and can impact cognitive development
- Testing demonstrated global developmental delays and many cognitive deficits
- Significant strength was evident in Franny’s visual memory
- Most concerning was that cognitive performance had declined
  
  NOT TYPICAL
- Comorbid hearing impairment made for additional challenges

References

Introduction

- Pseudotumor cerebri syndrome (PCS) is a progressive disorder marked by increased intracranial pressure without a known cause.
- A rare disorder in children, particularly prior to the age of 11
- Research on PCS related cognitive deficits have almost exclusively investigated adults.
- This presentation will provide a case study of childhood PCS

Previous Literature

- Limited research into cognitive implications of PCS
  - Adult studies ranging from 20y – 56y, with one 15yo included
  - Almost exclusively female
- Most common findings
  - General verbal deficits in language, memory, and fluency
  - General memory deficits
  - Executive dysfunction and poor cognitive flexibility
  - Slowed processing speed and reaction time
  - Visual-spatial deficits
- Most patients do not show cognitive improvement, despite treatment
- No patients show evidence of brain damage/malformation on CT/MRI to indicate cause of impairment

Tests Administered

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
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<tbody>
<tr>
<td>Intelligence</td>
<td>WISC-IV</td>
</tr>
<tr>
<td>Academic Achievements</td>
<td>Woodcock-Johnson Tests of Achievement, Fourth Edition (WJ IV)</td>
</tr>
<tr>
<td>Language</td>
<td>Boston Naming Test</td>
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<tr>
<td>Motor</td>
<td>Grooved Pegboard Test</td>
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<tr>
<td>Visuospatial</td>
<td>Benton Judgment of Line Orientation (JLO)</td>
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<tr>
<td>Memory</td>
<td>Test of Memory and Learning, Second Edition (TOMAL-2)</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>Delis-Kaplan Executive Function System (D–KEFS)</td>
</tr>
<tr>
<td>Behavior and adaptive functioning</td>
<td>Behavior Rating Inventory of Executive Function (BRIEF)</td>
</tr>
</tbody>
</table>

Pseudotumor Cerebri Syndrome (PCS)

- Symptoms
  - Mimics sx of brain tumor
  - Headache
  - Papilledema
  - Blurred vision
  - Increased CSF pressure
- Course
  - Develops over weeks or months
  - Absence of enlarged ventricles or a mass
  - Most common in obese adult women of childbearing age
- Treatment
  - Lumbar-peritoneal shunting
  - Lumbar puncture
  - Corticosteroids
  - Weight reduction

Case study: 12-year-old female “K”

Reason for Referral
- Memory difficulties
- Academic difficulties
- Impaired sense of time
- Impaired hygiene
- Fatigue and poor sleep

Demographics
- 6th grade with 504 plan
- Right-handed
- PCS diagnosed in 2011 (9yo)
- Papilledema
- Daily headaches
- BMI – 97th percentile

Developmental history
- Unremarkable pregnancy/birth
- Milestones achieved within normal limits
- Medical history unremarkable
- Current medical issues
  - Optic Nerve Drusen w/papilledema
  - 2-2 headaches per month
  - Snoring and daytime sleepiness
  - No prescribed medications
  - Unremarkable MRI/MS
  - Repeat studies

Surgical history
- Strabismus 2013, 2014
- Lumbar peritoneal shunt 2013

Results: Intelligence

WISC-IV

<table>
<thead>
<tr>
<th>Domain</th>
<th>Standard Score</th>
<th>Scaled Score</th>
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<tbody>
<tr>
<td>Verbal</td>
<td>76</td>
<td>10</td>
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<tr>
<td>Vocabulary</td>
<td>83</td>
<td>11</td>
</tr>
<tr>
<td>Comprehension</td>
<td>83</td>
<td>11</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>88</td>
<td>12</td>
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<tr>
<td>Block Design</td>
<td>76</td>
<td>10</td>
</tr>
<tr>
<td>Matrix</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>5</td>
<td>7</td>
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<tr>
<td>Letter Number</td>
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<td>8</td>
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<tr>
<td>Coding</td>
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<td>7</td>
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<tr>
<td>Total</td>
<td>73</td>
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</table>
Results: Academic Achievement

<table>
<thead>
<tr>
<th>Subject</th>
<th>Score</th>
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<tr>
<td>Calculation</td>
<td>94</td>
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<tr>
<td>Math Fluency</td>
<td>90</td>
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<tr>
<td>Applied Problems</td>
<td>70</td>
</tr>
<tr>
<td>Spelling</td>
<td>85</td>
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<tr>
<td>Oral Reading</td>
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<tr>
<td>Written Reading</td>
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Results: Language

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<tbody>
<tr>
<td>BNT</td>
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<tr>
<td>PPVT-4</td>
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<tr>
<td>EVT-2</td>
<td>88</td>
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Results: Visuospatial and Motor

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<th>Standard Score</th>
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<tbody>
<tr>
<td>Benton JLO</td>
<td>64</td>
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<tr>
<td>Berry Visual</td>
<td>85</td>
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<tr>
<td>Perception</td>
<td>72</td>
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<tr>
<td>Berry VMI</td>
<td>76</td>
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<tr>
<td>Pegboard Dom Hand</td>
<td>53</td>
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<tr>
<td>Non-Dom Hand</td>
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Results: Memory

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<thead>
<tr>
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<tbody>
<tr>
<td>Memory Verbal</td>
<td>75</td>
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<tr>
<td>Memory Visual</td>
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<tr>
<td>Work</td>
<td>75</td>
</tr>
<tr>
<td>Work Memory</td>
<td>70</td>
</tr>
<tr>
<td>Free Recall</td>
<td>70</td>
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<tr>
<td>VISL</td>
<td>70</td>
</tr>
<tr>
<td>VST L</td>
<td>70</td>
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<tr>
<td>VST R</td>
<td>70</td>
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Results: Executive Functioning

<table>
<thead>
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<th>Test</th>
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<tbody>
<tr>
<td>WCST Errors</td>
<td>109</td>
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<td>SCT Corp</td>
<td>50</td>
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<tr>
<td>Digit Span</td>
<td>85</td>
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<tr>
<td>Digit Span 2</td>
<td>85</td>
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<tr>
<td>Digit Span 4</td>
<td>90</td>
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<td>90</td>
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<tr>
<td>Digit Span 8</td>
<td>70</td>
</tr>
<tr>
<td>SST 2</td>
<td>85</td>
</tr>
</tbody>
</table>

Impressions

- Overall borderline impaired intellectual functioning and mildly impaired adaptive functioning
- Diffuse impairment in multiple areas of functioning
  - Comprehension
  - Memory across domains
  - Visual-perception and visual-construction
  - Motor speed/coordination
  - Confrontational visual naming/word retrieval
- Pockets of preserved cognition
Treatment Recommendations

- Changes to modifications/accommodations on implementation of IEP
- Strategies for slow learners emphasizing dividing tasks into smaller units, repetition with frequent practice
- Use of visual memory aids and routines to maintain consistency
- Mathematics tutoring and reading comprehension intervention
- Chart system for hygiene
- Referral to the Sleep Disorders Clinic

Case in Context

- In comparison to previous literature
  - Pattern of deficits were largely consistent with previous literature.
  - Particularly notable is her Borderline IQ with greater deficits in Verbal Comprehension – many adults did not have general impairments in IQ.
- Relevance to field
  - Although some view PCS as a “benign” condition, our findings suggest that diffuse cognitive deficits and impaired functioning are likely and will require intervention.
  - Will the condition become more prevalent in children as childhood obesity rises?

Questions

References


The Need for Collaboration

- Pediatric neuroimmunology is a rapidly changing field with many unknowns.
- Functional neurological symptoms are also poorly understood in children, and often considered only when medical causes are ruled out.
- This case highlights the need for collaboration between neuropsychologists and neurologists.
Demographics and Reason for Referral

- Kate: 12 year old Caucasian girl with suspected autoimmune encephalitis
- Normal early history until onset of symptoms two years ago
- Withdrew from rigorous private school in order to homeschool
- Participation in competitive gymnastics league
- Only child, living with both parents
- Family history noncontributory

Symptoms

- “Disney Princess” voice and mannerisms appeared following strep throat infection
- Approximately six months later developed additional neurological symptoms following urinary tract infection and flu mist vaccine
  - Dilated pupils
  - Agitation
  - Repetitive and tic-like behaviors
  - Dizziness
  - Headaches
  - Cognitive changes (memory, math, “brain fog”)
  - Slurred/pressured speech
  - “Emotional fatigue”
- Symptoms worsened and she was “almost comatose”

Medical Evaluations and Testing

- Multiple previous specialists
  - Neurology
  - Gastroenterology
  - Psychiatry
  - Infectious Disease
  - Chiropractic
  - Applied Behavior Analysis
  - Complementary and Alternative Medicine
- Negative strep titres
- Normal MRI of the brain
- Normal EEG
- Abnormal CSF results
  - Elevated interleukin 6 and 8
  - S100B of unclear significance

Treatments

- Injection of rocephin (symptom improvement for 24 hours)
- Intravenous immunoglobulin (brief improvement)
- Plasmapheresis (brief improvement)
- Scheduled to undergo additional intravenous immunoglobulin treatments

Initial Testing: Selected Scores

Performance on all tests represented as standard scores with higher scores reflecting optimal performance

Initial Testing: Parent Rating Selected Scores

Performance on all tests represented as standard scores with higher scores reflecting optimal performance

Impressions and Recommendations

- Autoimmune encephalitis
  - Continue with plan for intravenous immunoglobulin
  - Neuropsychological re-evaluation post-treatment
- Functional neurological symptoms
  - Consider psychotherapy for stress management and coping skills

**Two Months Later**

- Additional course of intravenous immunoglobulin completed
- No other treatments or changes
- Family reports improvements in symptoms
  - Memory problems and “brain fog”
  - Voice and mannerisms
  - Anxiety
- Improvements most noticeable immediately following treatment

Follow-Up Testing: Selected Scores


Impressions and Recommendations

- Autoimmune encephalitis
  - Further treatment planning deferred to neurology
- Functional neurological symptoms
  - Consider psychotherapy for stress management and coping skills
  - Mindful return to school
### Eight Months Later

- Enrolled in public school
- Non-competitive gymnastics club
- Noticeable improvements in voice and mannerisms
- Family complaints of residual mild memory deficits
- All other symptoms resolved

### Lessons Learned

- Assessment of rare neuroimmunological disease is inexact and ever-evolving, particularly in pediatrics
- Functional neurological symptom exacerbation can be considered alongside medical etiology
- Multidisciplinary collaboration can promote the best outcomes for patients and families

---

**Pediatric Grand Rounds**

Ashlee Loughan PhD  
Christen Holder PhD, Amanda Rach MS  
Alison Wilkinson-Smith PhD, Benjamin Greenberg MD  
Renee Lajiness-O’Neill PhD, Christine Salinas PhD,   
Michael Westerveld PhD, Philip Fastenau PhD