Advances in Tumefactive CNS Demyelinating Disease and Baló’s Concentric Sclerosis

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May 28th, 2015

Disclosures

► Honoraria for talks from Novartis, Genzyme, Merck
► Honoraria for chairing meetings from Genzyme
► Conference travel from Novartis, Biogen and Bayer-Schering
► Investigator Meeting travel from Alexion
► Advisory boards for Biogen, Merck
► Research monies from Novartis, Biogen and Genzyme
► Co-Editor, Advances in Clinical Neuroscience & Rehabilitation
Atypical Demyelination

- Schilder’s disease
- Haemorrhagic leukoencephalitis
- Solitary sclerosis
- Marburg’s disease
- Tumefactive demyelination
- Baló’s concentric sclerosis

What is tumefactive demyelination?

- Pseudotumoral demyelinating lesions > 2cm

Lesion of up to 12 cm have been reported. 

Jaffe & Minagar, 2005
Gaillard et al.
Luchinetti et al., 2008
Differential Diagnoses

- Primary neoplasm of the brain e.g. GBM
- CNS lymphoma
- Abscess
- PML
- Ischaemic stroke

Radiology – tumefactive demyelination

- Well circumscribed lesions
- Mild mass effect and perilesional oedema
- Mostly supratentorial white matter

Lucchinetti et al., 2008
Radiology

Most enhance (homogen, heterogen, nodular, punctate, ring)
Most have closed ring appearance
Open ring enhancement with incomplete portion of ring on gray matter side
Advancing area of active inflammation away from chronic central core

Modified from Guilfoyle and Kirollos, 2007
Radiology

- Other typical features include:
  - a T2 hypointense rim
  - peripheral restriction on DWI
  - venular enhancement

Multifocal and relapsing forms have been described

Among 54 patients with TD, 16.7% developed further TD lesions over 38 months.
Other conditions in which TD lesions described

► Viral infections including HIV
► Other autoimmune diseases such as SLE, Sjogren’s, Behcet’s disease
► Neuromyelitis optica (NMO)
► Drugs e.g. tacrolimus
► Malignancy; particularly renal cell carcinoma

Terminology

► Tumefactive demyelination NOT tumefactive MS
What is Baló’s concentric sclerosis (BCS)?

► Named after Joseph Baló in 1928

► “Encephalitis periaxalis concentrica”

Radiology of BCS

► Discrete, concentrically layered demyelinating lesion; “onion-ring” or whorled appearance

► Alternating isointense and hyperintense concentric rings on T2

► Lesion oedema is minimal
Radiology of BCS

- Gadolinium enhancement more likely at the peripheral aspect of the lesion
- Occasionally enhancement of multiple layers occurs corresponding to layers of T2 hyperintensity

Radiology of BCS

- Lesions most commonly in cerebral white matter
- Other sites include basal ganglia, pons and cerebellum
Magnetic resonance spectroscopy in TD and BCS

- Increased choline/NAA ratio also common in neoplasm Given et al. 2004
- Increased glutamate/glutamine but not extensively studied Cianfoni et al. 2007
- Serial MRS may be useful - as TD lesions age, their MRS findings change but remain stable in neoplasm Butteriss et al. 2003

CT-PET in TD and BCS

- May be a useful adjunct to MRI and CT
- Hypermetabolism less than in neoplastic lesions Schiepers et al. 1997; Takenaka et al. 2011
- A role for combined PET and MRS?

Takenaka et al. 2011
Epidemiology – TD and BCS

► Both TD and BCS are rare
► BCS more common in patients of East Asian origin (e.g. southern Han Chinese, Taiwanese and Filipinos)
► Female to male ratio of 1-2:1
► Peak incidence in 20s and 30s
► Paediatric and older patients have been described

Presentation TD and BCS

► Among 17 cases BCS from the Philippines, 50% had prodromal symptoms of mild fever, general malaise and headache (Tabira, 2009)

Lucchinnetti et al., 2008
When to biopsy?

► Without pre-existing diagnosis of MS
► Inconclusive/suspicious imaging
► Older or very young patients
► ?Negative OCBs

► If typical TD or BCS, treat as presumed demyelination and monitor clinically and radiologically

Hardy & Chataway, 2013

Case 1 - 2011

► 58 year old lady
► RRMS diagnosed in 1985
► Stable course with last relapse 1988
► Never required disease modifying therapy
► EDSS 1
Case 1

- P/w subacute onset of left hemiparesis
- No imaging performed in ED
- Given 3 days IVMP for presumed MS relapse
- Marked improvement

- 2 weeks later left hemiparesis worsens...

MRI brain

[Images of MRI brain scans]
Case 1 - Brain biopsy

► Glioblastoma multiforme

► *Don’t assume all tumefactive lesions in patients with MS are due to demyelination*
Pathology of TD

► Not greatly different from typical MS lesions
  - Pattern III Lucchinetti et al., 2008
► Demyelination with hypercellularity, reactive astrocytes ± multiple nuclei (Creutzfeld cells), foamy macrophages
► Relative axonal sparing with perivascular and parenchymal lymphocytic infiltrates

Pathology of BCS

► Alternating rings reflects areas of relative myelin preservation and loss with relative axonal sparing
► Some evidence for a mild astrocytopathy (Kira, 2011)
Rings of demyelination

Courville, 1970

Rings of demyelination

Agamanolis, 2012
Why are Baló lesions concentric?

(Stadelmann et al., 2005)

- Successive outward spread of a chemical mediator (e.g. cytokines, oxygen free radicals) in waves from a focal point
- A neuroprotective substance, secreted by attacked oligodendrocytes, prevents demyelination at the borders of the radially expanding lesion and preserves rings of relative demyelination
Further hypothesis (Kira, 2011)

► disruption between astrocyte and oligodendrocyte interaction leads to demyelination

Liesegang rings

aqueous salt diffuses through a gel containing another dissolved salt
Why are Baló lesions concentric? 
(Khonsari & Calvez, 2007)

► Mathematical modeling - non-linear chemotaxis of monocytes and microglia towards an unspecified chemoattractant

► Results in demyelination at areas where these effector cells congregate

Evidence that rings form sequentially 
(Kavanagh et al., 2006)

Restricted diffusion
Lindquist, 2007

Gadolinium enhancement

Kreft et al. 2009

Presentation 1 week 3 weeks 8 weeks

Lindquist, 2007

Kreft et al. 2009
What is the clinical relationship of BCS and TD to MS?

- Overlap more than just pathological
- Baló and TD lesions can occur during conventional RRMS
- ~55% who present with a Baló or Baló-like lesion will have typical MS lesions elsewhere on their MRI scan (Chaodong et al., 2008)

What is the clinical relationship of BCS to MS?

- 2 of 5 patients with initial Baló lesions relapsed with more typical MS lesions (Chaodong et al., 2008)
- Patients with Baló lesions and positive CSF OCBs can go on to develop MS (Kira, 2011)
- Among 11 patients with Baló-like lesions, CSF OCBs present in only one (Seewan et al., 2008)
BCS and TD in the same patient

Hardy et al., 2015

Acute treatment of TD and BCS

► No RCTs to guide

► **First line** - corticosteroids

► Largest case series >80% of TD patients respond to treatment with corticosteroid Altintas et al. 2012

► **Second line** - plasma exchange (PEX)

► Randomized trial - PEX beneficial in patients with mixed CNS inflammatory demyelinating disease who have failed to respond to corticosteroids Weinshenker et al. 1999
Refractory cases

► Rapidly expanding – consider PEX and corticosteroids together
► Risk of coning/brain herniation – decompressive craniectomy
► Rituximab (additional benefit of disease modifying effect)
► Cyclophosphamide and IVIg – perhaps more success in the paediatric population than in adults

DMT for TD and BCS

► Insufficient evidence to recommend or not recommend DMT
► Many clinicians favour using DMTs only after MS diagnostic criteria fulfilled
► Otherwise consider equivalent to a CIS
► But... DMT for CIS delays a second clinical attack and therefore conversion to MS
DMT in TD lesions

► Also, may be improvement in long term disability with early treatment of CIS
► Consider if high risk of conversion to MS e.g. OCBs +ve or multiple typical demyelinating lesions
► Shared decision making between an individual patient and their treating clinician

Hardy & Chataway, 2013

DMT in TD lesions

► Start with injectable (interferon beta or glatiramer acetate)
► TD lesions have been reported in patients with MS and NMO undergoing treatment with Natalizumab Berger, 2008; Twyman et al. 2010; Barnett et al. 2012
► One report of Natalizumab beneficial in a patient with rapidly evolving relapsing TD who - relapse-free at 12 months Seifert et al. 2012
Fingolimod

► TD in 5 patients switching from interferon or glatiramer to Fingolimod  

► 2 patients switching from Natalizumab to Fingolimod  
  Jander et al. 2013; Pilz et al. 2013

► 1 patient in FREEDOMS “haemorrhagic focal encephalitis” – no prior DMT  
  Leypoldt et al. 2009

More than just a chance association between TD lesions and Fingolimod?

► Reporting bias?

► Mechanism? – differentially reduce egress of inhibitory/regulatory cells from peripheral lymph nodes?  
  Visser et al. 2012; Castrop et al. 2012

► Role in treatment of TD to be determined

► A cautious approach is warranted
Prognosis of TD

► 39 patients – 54% complete recovery
Nagappa et al., 2013

► 85 patients with biopsy confirmed TD
Lucchinetti et al., 2008

► Time to second event in patients presenting with a TD lesion = 4.8 years
Kepes, 1993; Confraveux et al. 2012

► Slight trend for better prognosis when TD lesions accompanied by typical MS lesions on MRI
Lucchinetti et al., 2008
Prognosis of BCS – pre MRI

Courville, 1970

<table>
<thead>
<tr>
<th>No.</th>
<th>Report</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Survival period</th>
<th>Location of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Münch</td>
<td>1936</td>
<td>30</td>
<td>F</td>
<td>4 weeks</td>
<td>Right occipital lobe</td>
</tr>
<tr>
<td>2</td>
<td>Sumer</td>
<td>1926</td>
<td>19</td>
<td>F</td>
<td>2 years</td>
<td>Bilateral lesions</td>
</tr>
<tr>
<td>3</td>
<td>Kogler</td>
<td>1927</td>
<td>23</td>
<td>M</td>
<td>8 months</td>
<td>Bilateral</td>
</tr>
<tr>
<td>4</td>
<td>Babi</td>
<td>1927, 1928</td>
<td>23</td>
<td>M</td>
<td>12 months</td>
<td>Bilateral</td>
</tr>
<tr>
<td>5</td>
<td>Spiek (case 1)</td>
<td>1921</td>
<td>24</td>
<td>M</td>
<td>6 weeks</td>
<td>Bilateral</td>
</tr>
<tr>
<td>6</td>
<td>Pintér</td>
<td>1931</td>
<td>10</td>
<td>M</td>
<td>3 years</td>
<td>Bilateral</td>
</tr>
<tr>
<td>7</td>
<td>Barti and Van Bogaert</td>
<td>1933</td>
<td>30</td>
<td>F</td>
<td>3 weeks</td>
<td>Multiple large lesions</td>
</tr>
<tr>
<td>8</td>
<td>Waughner and Lowenberg</td>
<td>1933</td>
<td>17</td>
<td>M</td>
<td>3 months</td>
<td>Large unilateral lesion</td>
</tr>
<tr>
<td>9</td>
<td>Ule</td>
<td>1948</td>
<td>21</td>
<td>M</td>
<td>15 months</td>
<td>Frontal lesions</td>
</tr>
<tr>
<td>10</td>
<td>Zeman</td>
<td>1949</td>
<td>21</td>
<td>P</td>
<td>4 months</td>
<td>Bilateral</td>
</tr>
<tr>
<td>11</td>
<td>Hessen et al.</td>
<td>1950</td>
<td>33</td>
<td>M</td>
<td>7 months</td>
<td>Bilateral</td>
</tr>
<tr>
<td>12</td>
<td>Beba</td>
<td>1950</td>
<td>33</td>
<td>P</td>
<td>2 months</td>
<td>Bilateral</td>
</tr>
<tr>
<td>13</td>
<td>Ule and Kranew</td>
<td>1954</td>
<td>32</td>
<td>M</td>
<td>1 month</td>
<td>Basilar pons</td>
</tr>
<tr>
<td>14</td>
<td>Wagner</td>
<td>1956</td>
<td>29</td>
<td>P</td>
<td>7 weeks</td>
<td>Bilateral</td>
</tr>
<tr>
<td>15</td>
<td>Mage et al.</td>
<td>1958</td>
<td>19</td>
<td>M</td>
<td>2 weeks</td>
<td>Right basal ganglia</td>
</tr>
<tr>
<td>16</td>
<td>Ronal</td>
<td>1959</td>
<td>33</td>
<td>P</td>
<td>7 months</td>
<td>Parina</td>
</tr>
<tr>
<td>17</td>
<td>Örnell</td>
<td>1990</td>
<td>39</td>
<td>P</td>
<td>5 years</td>
<td>Bilateral cavitation</td>
</tr>
<tr>
<td>18</td>
<td>Ekelin</td>
<td>1991</td>
<td>39</td>
<td>M</td>
<td>4 months</td>
<td>Multiple lesions</td>
</tr>
<tr>
<td>19</td>
<td>Van Bogaert and Mackem</td>
<td>1993</td>
<td>31</td>
<td>M</td>
<td>1 year</td>
<td>Multiple lesions</td>
</tr>
<tr>
<td>20</td>
<td>Courville</td>
<td>1994</td>
<td>31</td>
<td>M</td>
<td>4 years</td>
<td>Basal ganglia – focal scar</td>
</tr>
</tbody>
</table>

Prognosis of BCS – MRI era

Hardy & Miller, 2014

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Isolated Babé or Babé-like lesions at presentation</th>
<th>Additional MS-like lesions at presentation</th>
<th>Number developing relapsing disease or MS</th>
<th>Number developing NMO</th>
<th>Follow-up*</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al, 1999**</td>
<td>5</td>
<td>ER</td>
<td>0</td>
<td>1-6 years (1-3)</td>
<td>100% survival</td>
<td></td>
</tr>
<tr>
<td>Keranen et al, 2004*</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>30 months (6-47)</td>
<td>100% survival with mild deficits</td>
</tr>
<tr>
<td>Chaboud et al, 2008B</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>8 years (4-13.5)</td>
<td>100% survival with mild or mild deficits</td>
</tr>
<tr>
<td>Wolven-Blank et al, 2013</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>12 years (0-2)</td>
<td>100% survival with mild or mild deficits (mean EDSS 1.5)</td>
</tr>
<tr>
<td>Scott, 2011*</td>
<td>6.5</td>
<td>17</td>
<td>NR</td>
<td>32</td>
<td>2</td>
<td>38% for &lt;2 years and 26% for &gt;2 years</td>
</tr>
<tr>
<td>Takacs, 2009F</td>
<td>17</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2-3 months (5-38 to 8 months)</td>
<td>100% mortality</td>
</tr>
<tr>
<td>Yao et al, 2004**</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1.8 months (35 days to 100 days)</td>
<td>100% mortality</td>
</tr>
</tbody>
</table>

Summary of published series since 1994. MS = multiple sclerosis; NMO = neuromyelitis optica; EDSS = Expanded Disability Status Scale score. *Scott has summarized data from published cases between 1999 and 2013. **Takacs and Yao and colleagues report data for all age cases only. *Data are mean (range) unless otherwise stated.

Table: Prognosis in patients with Babé’s concentric sclerosis
Why is prognosis better now?

► MRI - fuller appreciation of the genuine clinical spectrum?
► Earlier identification and treatment?
► Different disease processes i.e. true BCS vs ‘Baló-like’ lesions of conventional MS?

Conclusions

► Atypical demyelination is rare and poorly understood
► Potential for insights into lesion formation in conventional MS
► Future directions include:
  ► association with MS
  ► prognostic features
  ► treatment