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Blue Cone Signals in the Extra Striate Cortex: Explanation for Blind Sight?

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Our perception of vision is largely as a result of the signals conveyed from the eye to the brain via the retino-thalamo-cortical pathway. Visual signals within this pathway originate from three cone photoreceptors (responsible for day vision) and one scotopic receptor, the rods. The cones are classified according to their spectral sensitivity peaks as Long(L), Medium(M) and Short(S) wavelength sensitive cones. Our chromatic perception is dependent upon how the brain processes variations in the activity among these photoreceptors. Chromatic signals are generally thought to be processed by two parallel streams, the red-green system by the parvocellular system and the blue-yellow system by the koniocellular system. A large body of work has already been documented to identify these streams within the retina and the main thalamic visual nucleus, the Lateral Geniculate Nucleus (LGN). However, our knowledge about the processing of the chromatic signal within the visual brain, particularly the pathways taken by the blue-yellow colour signals within the brain is at its infancy.

Majority of relay cells within the LGN project to the primary Visual cortex (V1) and hence is considered vital for our visual perception. However, in some clinical cases, even after extensive damage to V1, patients have some residual vision. This phenomenon is called “blind sight”. The patients usually exhibit little or no awareness of visual stimuli, however can perform tasks that seemingly needs vision such as navigation. Most common hypothesis that has been postulated explaining this phenomenon is that blindsight is mediated by inputs to middle temporal area or area MT that bypass V1. Area MT remains active even after complete ablation or reversible inactivation of V1, suggesting that there are alternative pathways that bypass V1 to reach MT. Experiments with inactivation of the superior colliculus showed that one such pathway exists via the colliculus. Whether there is any evidence that blindsight is made up of chromatic signals is still unresolved. The perception of colour is usually associated with the “what” pathway as evident from area V4 often considered to be the area that processes color information and for being the gateway to the ventral pathway. Area MT, an extrastriate visual area is considered to be part of the “where” pathway and until recently was not considered to receive any colour signals but see Conway for a review of color signals in the dorsal and ventral pathways. However, more recent studies have shown that this area receives robust chromatic signal not only via V1 but also bypassing V1. Other studies have also shown that in subjects with blindsight found that within the hemianopic field, S-cone modulating stimuli were very effective in eliciting visual performance, and in fact in one patient presentation of narrow band blue stimuli (427 nm) led to excellent performance but not red stimuli (peaking at 630 nm). Thus, there is increasing evidence that S-cone signals reach area MT via a more direct route that bypasses V1 and providing an alternate explanation of blindsight in humans.

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CNS Complication of Group A Streptococcal Meningitis in Children: a Comprehensive Case-Based Literature Review

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ABSTRACT

Group A Streptococcus pyogenes meningitis rarely results in central nervous system complication. Chronic hydrocephalus is a well-known complication of bacterial meningitis. To date, no reports have focused on acute central nervous system complications and neurological outcome of Group A Streptococcus pyogenes meningitis. An unusual association of acute hydrocephalus requiring emergent neurosurgical intervention in a 6-year-old girl with Group A Streptococcus meningitis is presented. Based on reported cases since 1966, authors present the results of a comprehensive acute neurological complication and outcome. Our report highlights a need for vigilance and timely needed emergent surgical intervention in minimizing acute hydrocephalus in children with Group A Streptococcus meningitis.

KEYWORDS: Streptococcus pyogenes meningitis; Central Nervous System complication; Acute hydrocephalus; Surgical intervention; Children.

INTRODUCTION

Streptococcal infections are common in children. Unlike Group B Streptococci septicemia,1 Group A Streptococcus (S. pyogenes) typically affects children beyond the neonatal period. Occasionally, this causes acute meningitis, glomerulonephritis, or rheumatic heart disease.2 Group A Streptococcus infection is a rare cause of bacterial meningitis. Hydrocephalus is a relatively rare complication of acute bacterial meningitis in children. Nonetheless, it has been reported in 20% of infants and children. Acute Central Nervous System (CNS) complications including hydrocephalus are not unique to Streptococcus pyogenes causing meningitis. They have been reported in children with viral and other bacterial meningitis.³

We report an unusual association of acute hydrocephalus in a 6-year-old girl with Group A Streptococcal meningitis and provide the results of a comprehensive literature review on acute CNS complications and neurological outcome in children 17 years and under.
CASE REPORT

A 6-year-old girl presented to the Emergency Department with vomiting and neck pain for 24 hours. She had headache for five days and intermittent fever and sore throat for the past two weeks. She had no seizures and had received no antibiotics. A non-contrast Computerized Tomography (CT) scan of the brain prior to the lumbar puncture was normal. Treatment with intravenous vancomycin and ceftriaxone was initiated.

On admission to the Pediatric Intensive Care Unit, her vital signs were stable and temperature was 37.6 degree C. Her throat was red and congested but the tympanic membranes were normal. Her skin had no lesions. She had decreased alertness and her neck was hyper-extended in a fixed position. Pupils were 4 mm and reactive to light. Fundoscopic examination revealed no papilledema. Deep tendon reflexes were hyperreflexic and on plantar stimulation, her toes were up going.

The Cerebrospinal fluid (CSF) studies revealed an elevated intracranial pressure, a white blood cell count of 7644 mm$^3$, red blood cells 10,000 mm$^3$, protein 440 mg/dl and glucose 20 mg/dl. Serum glucose was 102 mg/dl. CSF smears revealed Gram-positive cocci in pairs and chains. The blood and CSF culture yielded *S. pyogenes*. Genotyping for the streptococcal isolates was not obtained. The CSF polymerase chain reaction for herpes simplex virus type 1 and 2 DNA for both, was negative.

Hospital Course

Ten hours after admission, she had an acute increase in heart rate from 80 to 133 beats per minute and blood pressure from 124/69 to 156/47 mm Hg. Her pupils became asymmetric and reacted sluggishly to light. Her Glasgow Coma Scale score declined from 13 to 9. Following endotracheal intubation, mechanical ventilation, and administration of 1 gram/kilogram of mannitol, a contrast-enhanced brain CT scan was performed which revealed communicating hydrocephalus with no herniation or abscess (Figure 1A). An urgent frontal external ventricular drain was placed. A follow up brain CT scan revealed relief of the hydrocephalus (Figure 1B).

The ventriculostomy tube was clamped on day 12 and was removed on day 15. Intravenous ceftriaxone was continued for 21 days. She received physical, occupational, and speech therapies throughout the hospitalization. She was discharged on the 23rd day of admission with no focal motor, cerebellar, or sensory deficits.

DISCUSSION

Increased intracranial pressure caused by communicating hydrocephalus may be the result of long standing hydrocephalus, increased CSF production, decreased CSF absorption, or tonsillar herniation. Streptococcal infection produces many virulence factors and toxins.

A clinical and epidemiologic study for the last 45 years reported the incidence of GAS meningitis in pediatric population 0.06 cases per 100,000 children per year. The case fatality rate was 43%. Neonatal age and the presence of an associated toxic shock syndrome were identified as risk factors for death. A distant focus of infection was present 36% in the Brazilian case series which were more than half of the patients in the literature. No single virulence determinant could be associated with death.

Literature Search and the Results

We performed PubMed online search for English literature for *Streptococcal pyogenes* meningitis in children 0-17 years and under. We used terms “Group A Streptococcal meningitis”, “Streptococcal pyogenes meningitis”, “with and without” and “CNS complications” and “acute and chronic hydrocephalus” with a variable combination. Bibliography of the reports was searched for additional information.

The results of our literature search with CNS complications are shown in Table 1.

Clinical Demography

With the exception of 7 neonates, the mean age for children with CNS complications was 6.1 years. Of 44 children, 30 (68%) children had a known focus of infection. In fourteen (32%) children the focus of infection was unknown.
<table>
<thead>
<tr>
<th>Case #</th>
<th>Age/ Sex</th>
<th>Infection Focus</th>
<th>Central Nervous System Complication</th>
<th>Year [Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 d/M</td>
<td>Erysipelas</td>
<td>Seizures</td>
<td>1966&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>8 d/M</td>
<td>Unknown</td>
<td>Seizures</td>
<td>1967&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>13 d/F</td>
<td>Cellulitis of both feet</td>
<td>Focal Seizures</td>
<td>1984&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>14 d/F</td>
<td>Cystic gingival lesion</td>
<td>Seizures, No sequelae</td>
<td>1983&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>24 d/F</td>
<td>Unknown</td>
<td>Seizures, Brain Abscesses</td>
<td>2000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>26 d/M</td>
<td>Paronychia</td>
<td>Seizures, Communicating Hydrocephalus</td>
<td>No sequelae</td>
</tr>
<tr>
<td>7</td>
<td>28 d/M</td>
<td>Unknown</td>
<td>Seizures and Brain Abscess</td>
<td>No sequelae</td>
</tr>
<tr>
<td>8</td>
<td>1 m/F</td>
<td>Unknown</td>
<td>Seizures</td>
<td>1967&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>1 m/F</td>
<td>Unknown</td>
<td>Meningitis and Multiple Brain Abscess</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>1.5 m/M</td>
<td>Otitis Media</td>
<td>Seizures</td>
<td>1979&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>NA/NA</td>
<td>Unknown</td>
<td>NA</td>
<td>1986&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>2 m/M</td>
<td>Tonsillitis</td>
<td>Seizures and Subdural effusions</td>
<td>Moderate Motor Deficit, Cystic Hygroma</td>
</tr>
<tr>
<td>13</td>
<td>2 m/NA</td>
<td>Ulcerated and Infected heman-gioma</td>
<td>Infantile spasm and Seizures</td>
<td>Encephalomalacia, Infantile spasms, Profound Developmental Delay</td>
</tr>
<tr>
<td>14</td>
<td>2.5 m/M</td>
<td>None</td>
<td>Seizures and SIADH</td>
<td>Seizure Disorder, Optic atrophy, Microcephaly, Psychomotor Retardation</td>
</tr>
<tr>
<td>15</td>
<td>2.5 m/F</td>
<td>Infected heman-gioma</td>
<td>Seizures</td>
<td>Psychomotor Retardation</td>
</tr>
<tr>
<td>16</td>
<td>2.5 m/M</td>
<td>Pharyngitis</td>
<td>Focal Seizures</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>17</td>
<td>3 m/M</td>
<td>Infected BCG *scar</td>
<td>Generalized Seizures</td>
<td>No sequelae</td>
</tr>
<tr>
<td>18</td>
<td>3 m/F</td>
<td>Chicken pox</td>
<td>Hydrocephalus</td>
<td>No sequelae</td>
</tr>
<tr>
<td>19</td>
<td>7 m/F</td>
<td>None</td>
<td>Seizures</td>
<td>1992&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>20</td>
<td>11 m/NA</td>
<td>Unknown</td>
<td>NA</td>
<td>Bilateral Subdural Hydrocephalus</td>
</tr>
<tr>
<td>21</td>
<td>17 m/M</td>
<td>Otitis media</td>
<td>Generalized Seizure, Brain Abscess</td>
<td>No sequelae</td>
</tr>
<tr>
<td>22</td>
<td>18 m/M</td>
<td>Dermal sinus of nose and Otitis Media</td>
<td>Recurrent Meningitis</td>
<td>No sequelae</td>
</tr>
</tbody>
</table>
Table 1: Lists increasing age-based case Reports of central nervous system (CNS) complications in children with Group A Streptococcal meningitis since 1966 [6-38].

d: days; M: male; F: female; m: month; yr: year;
aNA, data not available; bSIADH, Syndrome of Inappropriate Anti-Diuretic Hormone;
cBCG, Bacillus Calmette–Guérin

The table is based on the results of our search on PubMed for English literature for children age 17 years and under with central nervous system complications caused by Streptococcal A meningitis. Our search identified 40 studies with 43 children, excluding the current report (Case # 30). Twenty seven (68%) studies were isolated case reports. Six reports reference number 7, 9, 22, 32, 38 and 8, had 2 cases each. The study number 8 included 6 cases. The children who presented with meningeal manifestations of headache, photophobia, and neck stiffness, but no CNS complications were excluded from this report.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Condition</th>
<th>Complications</th>
<th>Outcome</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>2.5 yr/M</td>
<td>None</td>
<td>Seizures and Increased intracranial pressure</td>
<td>Death</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>3 yr/M</td>
<td>Otitis media</td>
<td>Seizures</td>
<td>Partial blindness, Deafness, Mental Retardation</td>
<td>1984</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>3.5 yr/M</td>
<td>Pharyngitis and Mastoiditis</td>
<td>Cerebral Abscess</td>
<td>Left sensorineural hearing loss</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>4 yr/M</td>
<td>Otitis media</td>
<td>SIADH</td>
<td>No sequelae</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>4.5 yr/NA</td>
<td>Cochlear implantation</td>
<td>Hearing loss</td>
<td>Language Delay</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>5 yr/NA</td>
<td>Right Mastoiditis</td>
<td>Right Facial Nerve Palsy</td>
<td>No sequelae</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>6 yr/NA</td>
<td>Unknown</td>
<td>NA</td>
<td>Cranial Nerve IV Palsy</td>
<td>1976</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>6 yr/F</td>
<td>Pharyngitis</td>
<td>Communicating hydrocephalus</td>
<td>No sequelae</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>8 yr/M</td>
<td>Otitis media, Pneumonia</td>
<td>Seizures</td>
<td>Neuropsychological deficit</td>
<td>1981</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>8 yr/M</td>
<td>Sore throat</td>
<td>Seizures</td>
<td>No sequelae</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>8 yr/F</td>
<td>Unknown</td>
<td>Coma</td>
<td>No sequelae</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>8 yr/F</td>
<td>Unknown</td>
<td>(Toxic Shock-Like Syndrome)</td>
<td>Death</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>8 yr/M</td>
<td>Otitis Media, Pharyngitis</td>
<td>Subdural effusion, Hemiparesis, and Seizures</td>
<td>Headaches and Attention Deficit Disorder</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>10 yr/M</td>
<td>Unspecified illness</td>
<td>Brain Abscess</td>
<td>No sequelae (abscess required surgical drainage)</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>11 yr/NA</td>
<td>Multiple Otitis media</td>
<td>Cranial Nerve III Palsy</td>
<td>Cranial Nerve III Palsy, Subdural Hygroma</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>12 yr/F</td>
<td>Pharyngitis, Otitis media</td>
<td>Coma and Hemianopia</td>
<td>Persistent Hemianopia</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>12 yr/F</td>
<td>None</td>
<td>Brain Abscess</td>
<td>No sequelae</td>
<td>1988</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>13 yr/F</td>
<td>Sinusitis</td>
<td>Seizures</td>
<td>Moderate Motor Deficit</td>
<td>1992</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>14 yr/NA</td>
<td>Posttraumatic meningitis</td>
<td>Cerebrospinal fluid leak</td>
<td>Severe Psychomotor Retardation</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>15 yr/M</td>
<td>Occipital Fracture</td>
<td>Cerebrospinal fluid leak</td>
<td>No sequelae</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>15 yr/F</td>
<td>Tonsillitis</td>
<td>Seizures and Cerebral abscess</td>
<td>No sequelae</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>17 yr/M</td>
<td>Pharyngitis, sinusitis</td>
<td>Cavernous Sinus Thrombosis</td>
<td>No sequelae</td>
<td>1999</td>
<td></td>
</tr>
</tbody>
</table>
or was not described. Amongst children with known focus, 13 (43%) had otitis media and/or pharyngitis. Tonsillitis, infected hemangioma, cellulitis, or erysipelas, and 1 patient had sore throat. Other minor but significant foci of infection included skull fracture, infected dermal sinus, and mastoiditis.

**Central nervous system complication**

The most common acute CNS complication secondary to *Streptococcal* meningitis was seizure 24/44 (55%) followed by brain abscess 8/44 (18%). Other acute complications included hydrocephalus, CSF leak, meningitis, cranial nerve palsy and subdural effusion, except one case, the complication was unknown.

**Neurological Outcome**

Regarding outcome, 18/44 (41%) patients including ours had no sequelae. 10/44 (23%) cases developed a slowing of speech or physical movement with or without a decreased cognitive ability, 3/44 (7%) cases with hearing loss, 2/44 (4.5%) cases with cranial nerve palsy, 2/44 (4.5%) cases developed partial or complete blindness, only 1/44 (2.3%) developed chronic hydrocephalus. In one case the outcome was unknown (See Bar Graph).

In addition, 7/44 (16%) children died from complications of Group A Streptococcus meningitis, secondary to cardio respiratory insufficiency, Waterhouse Friderichsen syndrome, and Toxic shock-like syndrome. It is unclear why previously healthy children with Group A streptococcus meningitis developed significant CNS complications?

In contrast to our case, two previous cases of acute hydrocephalus were reported during early infancy. Acute onset hydrocephalus in our case was likely due to the combined effect of untreated prolonged pharyngitis, and initial delay in diagnosis and treatment. We suggest that a high CSF protein together with pleocytosis impeded absorption of CSF by arachnoid villi at the superior sagittal sinus. Such functional blockage causing chronic hydrocephalus has been reported in the presence of proteinaceous and cellular debris in CSF and also after intracranial hemorrhage.

Alternatively, the term “communicating hydrocephalus” which could be acute or chronic is defined to mean that the CSF within the ventricles communicating with subarachnoid space CSF. But the CT scan panel A shows CSF within the ventricles and an obliterated subarachnoid space. Arguably, there is no evidence that the ventricles and subarachnoid space are in communication with each other (a broader definition of obstructive hydrocephalus), and therefore, this is not “communicating hydrocephalus”. Additionally, hydrocephalus is not caused by increased CSF production or by tonsillar herniation. Instead, in our case, the non-communicating hydrocephalus is caused by ventriculitis resulting in obstruction to the outflow of CSF through the fourth ventricle.

**CONCLUSION**

Our case illustrates that Group A Streptococcal meningitis induced acute hydrocephalus is rare. A timely instituted surgical intervention may prevent other CNS complication. The review of published cases reveals that central nervous system complications including hydrocephalus are
rare. Since prompt antibiotic therapy can minimize risk for acute CNS complications, prompt identification and emergent medical and neurosurgical interventions should be undertaken for an optimum outcome in children with Group A streptococcal meningitis.

ACKNOWLEDGEMENT

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CONFLICTS OF INTEREST

The authors have no financial considerations to disclose or competing interests in relation to this article.

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Review

'Lipocalin-2 in Stroke

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ABSTRACT

Stroke is a leading cause of adult disability in the United States. However, limited number of molecularly targeted therapy exists for stroke. Recent studies have shown that Lipocalin-2 (LCN2) is an acute phase protein mediating neuroinflammation after ischemic and hemorrhagic strokes. This review is an attempt to summarize some LCN2-related research findings and discuss its role in stroke.

KEYWORDS: Lipocalin-2; NGAL; 24p3; Stroke; Reperfusion injury; Neutrophil; PKC; Phosphorylation; Biomarker.

INTRODUCTION

Stroke is a sudden loss of neurological function due to ischemia or hemorrhage in the brain.1 It is the fifth leading cause of death and a major cause of long-term disability in the United States.2 There are two main types of stroke: ischemic and hemorrhagic strokes. Ischemic stroke accounts for approximately 87% of all strokes and results from blockage of blood flow into the brain by thrombus or embolus. Hemorrhagic stroke, caused by rupture of cerebral blood vessels, is less common (13%) than ischemic stroke but accounts for 50% of stroke death.3-6 Currently, there is no proven medical or surgical treatment for hemorrhagic stroke. Thrombolysis with fibrinolytic agents such as tissue Plasminogen Activator (tPA) is the only FDA approved therapy to reverse ischemic stroke.7 However, only 5% of patients receive the treatment because tPA must be given within 3 to 4.5 hours after the occurrence of stroke. Delayed treatment may increase the risk of serious side effects such as hemorrhagic transformation and reperfusion injury.8 Ischemia initiates cerebral infarction during ischemic stroke, but reperfusion after recanalization may promote secondary injury and worsen neurological outcomes.8,9 Reperfusion injury includes a series of inflammatory events with activation and infiltration of circulating neutrophils, macrophages, and T-cells into infarcted brain tissue.10,11 Post-stroke inflammation has detrimental effects, but may be needed for repairing processes.11 In order to reduce stroke-reperfusion injury and develop effective and balanced therapeutic methods, it is important to identify neurotoxic and neuroprotective molecules of post-stroke inflammation. In the acute stage of stroke (within 24 hours), infiltrating immune cells release proinflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines (MCP-1, MIP-1α, IL-8), reactive oxygen species (ROS), and matrix metalloproteinase (MMP) (mainly MMP-9), which amplify neuroinflammatory responses and lead to brain edema, neuronal death, and disruption of blood-brain barrier (BBB).6,8,11 However, some of these molecules have a different role in the later stage of stroke (after 24 hours). For example, MMP-9 enhances ischemic brain injury, BBB leakage, and hemorrhagic transformation in the acute stage, but facilitates regeneration and remodelling of brain tissues in the later stage of stroke.12 Therefore, detailed mechanistic studies of post-stroke inflammation are needed.
LIPOCALIN-2 (LCN2) IN ISCHEMIC STROKE

Lipocalin-2 (LCN2), also known as 24p3 or neutrophil gelatinase-associated lipocalin (NGAL), is a 25 kDa protein secreted from activated neutrophils.\(^\text{13}\) Using a chemical-genetics approach, LCN2 was identified as one of PKC\(\delta\) phosphorylation substrates in neutrophils.\(^\text{14-16}\) PKC\(\delta\) directly phosphorylates LCN2 at Thr-115, and mediates the secretion of LCN2 from activated neutrophils in vitro and after cerebral ischemia in vivo.\(^\text{16}\)

Plasma level of LCN2 is elevated at 1-3 days in patients with ischemic stroke.\(^\text{17-19}\) LCN2 is acutely induced after transient middle cerebral artery occlusion (tMCAO) in rodents (a model of ischemic stroke).\(^\text{20-22}\) LCN2 appears in mouse sera as early as one hour, peaks at 23 hours, and diminishes by 48 to 72 hours after tMCAO.\(^\text{23}\) Due to the short time window for effective thrombolytic therapy, it is of great interest to diagnose stroke early and reduce the risk of cerebral hemorrhage.\(^\text{24,25}\) The early induction of LCN2 suggests the possibility of using LCN2 as an early blood biomarker to detect stroke.

In addition to blood plasma, LCN2 is also induced in the penumbra of ipsilateral hemispheres after tMCAO.\(^\text{21-23,26}\) The induction of LCN2 in mouse brain initiates at 6 hours, reaches a peak at 24 hours, and reduces at 48 hours after reperfusion. Induced LCN2 protein is identified in a subset of reactivated astrocytes, cerebral endothelial cells, and infiltrated neutrophils after tMCAO.\(^\text{21,23,26}\) Cerebral infarction, neurological deficits, infiltration of immune cells, BBB permeability, proinflammatory cytokines, chemokines, and adhesion molecules are reduced after tMCAO in LCN2 null mice.\(^\text{21,23}\) Recombinant LCN2 protein is able to stimulate neutrophil migration as well as promote cell death in primary neurons but not in astrocytes, microglia and oligodendrocytes.\(^\text{21,23,27,28}\) These results suggest that LCN2 is a proinflammatory mediator during the acute stage of ischemic stroke. Therefore, LCN2 inhibitors or anti-LCN2 antibodies may prove useful to reduce post-stroke inflammation and brain injury. At later time point (3 days) after ischemic stroke in rats and humans, LCN2 is expressed in injured neurons and may be released as a “help me signal” to condition microglia and astrocytes for recovery.\(^\text{22}\) These studies demonstrate the diverse functions of LCN2 during the acute and later stages of ischemic stroke.

LIPOCALIN-2 (LCN2) IN HEMORRHAGIC STROKE

Hemorrhagic stroke is a devastating form of stroke with high mortality.\(^\text{3,4,5}\) There are two major types of hemorrhagic stroke: intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). ICH is associated with bleeding in the brain parenchyma.\(^\text{6}\) SAH is often caused by intracranial aneurysm with blood leakage in subarachnoid space.\(^\text{7}\) LCN2 is induced mainly in astrocytes after rodent models of ICH and SAH.\(^\text{8,9}\) LCN2 induction was detected in the ipsilateral hemispheres at 1, 3, 7 days after ICH in rats and 24 hours after SAH in mice.\(^\text{8,9}\) Iron overload after ICH induces perihematoma edema and brain injury.\(^\text{10,11}\) LCN2 is capable of transporting iron through siderophore.\(^\text{12,13}\) Injection of iron upregulates the expression of LCN2 in the brain, while systemic treatment of an iron chelator (deferoxamine) reduces ICH-induced LCN2 upregulation.\(^\text{13}\) The results suggest that LCN2 may function as an important regulator of iron homeostasis after ICH. White matter injury and markers for axonal damage and myelin degradation are increased after SAH in wild type mice, but scarcely developed in LCN2 null mice.\(^\text{14}\) The result suggests that LCN2 may facilitate the development of white matter injury after SAH.

Several studies summarized in this review suggest that LCN2 promotes brain injury as a proinflammatory molecule in the acute stage of stroke.\(^\text{15-17,21,23,26,29,30}\) Interestingly, LCN2 may also support the neurovascular recovery by enhancing angiogenesis and serving as a “help me signal” in the later stage of stroke.\(^\text{31}\) Therefore, a comprehensive understanding of time-dependent functions of LCN2 is a prerequisite for developing effective therapeutic interventions for the treatment of ischemic and hemorrhagic strokes.

CONCLUSION

LCN2 has been identified as an important mediator of stroke-reperfusion injury and white matter injury after ischemic and hemorrhagic strokes. Future studies are needed to reveal the detailed mechanisms of LCN2-mediated signaling and to develop potential LCN2-based therapy.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES


Astrocyte: A Potential Target for the Treatment of Anorexia Nervosa

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Without homeostatic control of feeding behavior, energy balance will be disturbed towards either energy surplus or deficit, respectively, leading to obesity or wasting. Anorexia Nervosa (AN) is a disorder characterized with food restriction and weight loss due to intense fear of gaining weight and a distorted perception of body weight. The individuals with anorexia believe they are fat and seek to prevent weight gain by restricting the amount of energy intake even when they are starvation. Anorexia and its associated disorders impose a huge burden to our society, so treating and reversing anorexia are of paramount importance. However, the underlying mechanisms of anorexia are poorly understood, and there is a lack of effective treatments.

The nervous system consists of two classes of cells, neurons and glia. Thus, it is important to define the integrative processes of neurons and glial cells in the brain regions that control food intake. It is well recognized that neurons play critical roles in controlling feeding behavior and appetite, while little is known about glial influences on feeding. Astrocytes, the most abundant glial cells in the brain, are closely associated with neuronal synapses to scale synaptic strength and modulate neural circuits, as well as with cerebral blood vessels to adjust blood supply. Emerging evidence demonstrates the functional role of astrocytes in complex behaviors. Interestingly, in response to high-fat diet (HFD) feeding, astrocytes in the ARC proliferate and express functional receptors for leptin, adipocyte-derived anorexigenic peptide. These studies strongly suggest the involvement of astrocytes in the regulation of appetite.

In the hypothalamic arcuate nucleus, AgRP (Agouti-related peptide) neurons are necessary and sufficient to rapidly evoke food intake while POMC (Pro-opiomelanocortin) neurons inhibit feeding. The electrical activities of the neurons are critical for them to regulate food intake. Prior studies demonstrate that both of the two types of neurons in the ARC receive synaptic inputs, and glutamatergic excitatory synaptic inputs are crucial for neuronal firing. We thus propose that astrocytes in the ARC could serve as surveyors of hunger states and in turn modulate feeding by rewiring the appetite control circuits in the ARC. In anorexic mice, astrocytes may negatively regulate feeding by reducing synaptic strength at and the firing rate of orexigenic AgRP neuron through release of the inhibitory gliotransmitter(s), such as adenosine. Adenosine in turn inhibits synapse transmission and neuron firing rate by acting on A1 receptors in both pre- and post-synaptic neurons. Collectively, we propose that glial cells may actively participate in regulating energy balance by modulating appetite control circuits. It is well recognized that hypothalamic arcuate nucleus is a key brain region that control energy intake and energy expenditure. In our recent studies, we find that food intake is also under the control of astrocytes. For instance, we find that the food intake is reduced by selective chemogenetic activation of astrocytes localized in the mediobasal hypothalamus in mice.

Collectively, these results indicate that glial cells may also, at least in part, contribute to the development of anorexia nervosa. Furthermore, emerging evidence indicates that appetite is also under the control of “higher level” brain structures, such as cortex and hip-
pocampus, well-recognized brain regions implicated in emotion and cognition. For instance, lesion of ventral hippocampus reduces appetite, indicating that ventral hippocampus exerts tonic inhibition on food intake. To fully understand the control of food intake and seek effective clinical therapeutics to treat appetite disorders, such as anorexia nervosa, it is of importance to consider both neuronal and glial processes localized in multiple brain regions.

REFERENCES


Radiation Therapy and Nimotuzumab in Children and Adolescents with Brainstem Gliomas: A 5-Year Institutional Experience

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ABSTRACT

Background: Brainstem gliomas (BSG) are Central Nervous System (CNS) tumors with a median survival time of approximately 9 months. Up to now chemotherapy has not shown to improve survival in these patients. The outcome of Radiation Therapy (RT) in combination with Nimotuzumab is shown in the present report.

Material and Methods: 28 children and adolescents were included between Jan/2009 and Dec/2012 with the diagnosis of BSG and follow-up till January 2015. All patients had Diffuse infiltrative Pontine Gliomas (DIPG) and were irradiated with a dose ranging from 54 to 59.6 Gy at the National Oncology and Radiobiology Institute in Havana, Cuba. Three patients were planned with IMRT and 25 with 3D Conformal RT. Nimotuzumab was indicated at the dose of 150 mg/m² weekly during the time of RT treatment, then every 15 days during 8 weeks and finally monthly for 1 year. Univariate and multivariate Cox regression models and Kaplan Meier survival were analyzed to evaluate the survival.

Results: Median age at diagnosis was 7 years (range 3-18 years old), median overall survival was 17.3 months (95% CI 14.0-20.5) since the beginning of the treatment and the accumulated survival at 5 years of treatment was 42.9%. There was balance in sex, age and dosage of RT in the population. Addition of Nimotuzumab to RT was safe.

Conclusions: The combination of Radiotherapy and Nimotuzumab were well tolerated in this brainstem tumours patient’s series.

KEYWORDS: Radiotherapy; Nimotuzumab; Brainstem tumors children adolescents.

INTRODUCTION

The brainstem is defined as the midbrain, pons and medulla; brainstem gliomas are generally diffuse intrinsic tumors involving the pons, with defined clinical presentation and characteristic appearance in imaging findings and do not require pathological confirmation;¹⁻⁴ it can extend along neural tracts to adjacent regions of the brain, so it has been defined as fatal disease. Radiation treatment response rates show low degrees of efficacy, with short-term responses and a median overall survival less than one year;⁵⁻⁸ Diffusely infiltrating pontine glio-
mas must be distinguished from other subsets of diffuse intrinsic pontine gliomas, such as focal tumors, which are described with better prognosis and longer term survival.\textsuperscript{5,9}

The association of Chemotherapy (ChT) and radiotherapy (RT) have not improved survival\textsuperscript{1,6-8,10,11} and now biologics are combined with RT in clinical trials.\textsuperscript{9,12,13}

We investigated the association of RT with Nimotuzumab, a humanized monoclonal antibody developed at the Center of Molecular Immunology, Havana, Cuba and testing the hypothesis that this combination will improve survival in these tumors. The antibody was obtained by humanization of the murine antibody EGF/R3.\textsuperscript{14} Because Nimotuzumab has a 10 fold lower affinity to the EGFR, as compared to cetuximab, its capacity to bind EGFR is heavily dictated by cell receptor density.\textsuperscript{15} Nimotuzumab preclinical and clinical characterizations have been summarized before.\textsuperscript{16-18}

A distinguishing feature of Nimotuzumab compared to other mAbs of the EGFR class is the lack of severe skin toxicity and the possibility to be used beyond progression.\textsuperscript{16,19}

**MATERIAL AND METHODS**

We conducted a prospective, non-randomized clinical study, with a treatment group of 28 children and adolescents (range 3 to 18 years) with the diagnosis of diffuse intrinsic pontine glioma (DIPG) documented by imaging (MRI, CT scan.). Biopsy and histology confirmation were not a requirement of this study. This study covers a sequential period between Jan/2009 and Dec/2012. Follow-up continued to September 2014. Patients with focal lesion of the brainstem were not eligible for the study, because these are described with a better prognosis.\textsuperscript{5,9} Also excluded were those who had received prior chemotherapy or radiotherapy.

The study was approved by the Ethical Institution Committee at the National Oncology and Radiobiology Institute (INOR), Havana and informed consent obtained from the patients’ parents. All patients were irradiated at INOR, and received the monoclonal antibody Nimotuzumab at INOR or at the Pediatric Hospital “Juan Manuel Marques”, also in Havana. Male patients: 14, and female: 14.

No surgical treatment was feasible, and in 3 there were pathologic results by biopsy. In all patients tumor was extended to the pons.

Linear Accelerator was used for a radiation treatment: Gross Tumour Volume (GTV) was defined as the visible tumor, either by MRI or CT; Clinical Target Volume (CTV) accounted for subclinical microscopic disease and unappreciated tumor extension, generally 1.5 cm from the GTV, and Planning Target Volume (PTV) was 0.3-0.5 cm and could vary according to the Organ at Risk.\textsuperscript{4,20} RT doses range from 54 to 59.8 Gy, with dose per fraction 1.8 Gy. Three patients were planned with IMRT and the rest with 3D CT. In all patients a thermoplastic mask was fitted.

Nimotuzumab was administered at a dose of 150 mg/m\textsuperscript{2} (IV), weekly during the term of RT, then every 2 weeks for 8 doses, then monthly for one year. In the last patients included it was prolonged for 2 years.

Twenty four patients (85.7\%) received the complete Nimotuzumab schema, in 4 there were minor interruptions of the dosage because patients did not concur with the treatment option in a timely manner. Characters of the series are in Table 1.

| Median age at diagnosis……………….. 7 years old ( range 3-18 years ) |
| Male/female ratio………………………… 1:1 |
| Type of tumor……………………………DIPG-28 |
| Localization……………………………………Mid brain and pons: 15 |
| ..............................................Pons:6 |
| Not specified: 3 |
| Pathology……………………………………Grade II Astrocytoma:2 |
| ..............................................Grade III Astrocytoma: 1 |
| Not biopsied: 25 |
| Radiotherapy dose received………………….54-57 Gy : 4 patients |
| ..............................................57-59 Gy: 15 patients |
| ..............................................59, 8 Gy: 9 patients |
| Nimotuzumab treatment…………………………….Completed: 24 |
| Not completed: 4 |

Table 1: Charts of the series of brainstem gliomas in children and adolescents.

Univariate and multivariate Cox regression models were fitted in order to identify possible predictors of survival and Kaplan Meier survival was calculated for all cases.

**RESULTS**

Median age of the cases at diagnosis was 7 years (range between 3 and 18 years old). Twenty eight cases were DIGP, but in all cases tumor extended to pons, and in one case also to 4th ventricle, cerebellum and hypothalamus.

The diagnosis was made by clinical and imaging findings except in 3 cases where pathological examination was also done, one with astrocytoma grade II and the 2 others with astrocytoma grade III, all alive. Median overall survival from the beginning of treatment was 17,3 months, 95% CI (14.1-20.7) and Kaplan Meier survival accumulated was 42.9\% at 2 years, established till 5 years of RT treatment. At present, (January
2015) 12 of the patients are alive (2 less than 2 years, 3 between 2-3 years, 5 between 4-5 years and 2 with more than 5 years of follow-up). Therapeutic results were compared with a previous case series of 22 children and adolescents with BSG treated with the same mode of irradiation, but without Nimotuzumab during 1992-2008 at the same institution (Instituto Nacional de Oncología y Radiobiología in Havana.) (Figure 1)

**Sex**

14 female patients had a 44.0% survival at 2 years and counting, and 14 male patients a 33.3 % survival. (Figure 2)

Five patients received a dose between 54-57 Gy, with a survival rate of 60% at 2 years and counting; 16 patients with a dose between 57-59 Gy with a survival rate of 41.2 % at 2 years plus, and 7 patients received 59.8 Gy with a survival of 22.2% at 2 years plus. Radiation dose was increased in those patients where DIPG tumor size exceeded the mean. (Figure 3)

**By Age Group**

6 patients in the group up to 4 years old (21.5%) with a survival rate of 25% at 2 years plus; 15 patients between 5-9 years old (53.6%) with a survival rate of 37.5% at 2 years plus; 4 patients between 10-14 years old (14.4%) with a survival rate of 67%; and 3 patients with 15-18 years old age (10.7%) with a survival rate of 50% at 2 years plus (Figure 4).
Multivariate analysis showed no significant differences according to sex, age and dose of irradiation received, nor with the dosage of Nimotuzumab, with a tendency for best survival in age group 10-18 years old and with the dose at 54-57 Gy.

Treatment was well tolerated and no grade III or higher grade toxicity was observed. The most frequent adverse event was alopecia in irradiation fields, observed in 27 patients (96.4%). Other reported adverse events were vomiting, headache, fever, tremor and nausea, in less than 40% of patients (Table 2).

<table>
<thead>
<tr>
<th>Most frequent related adverse events</th>
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<tr>
<td>Severity grade</td>
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<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Headache</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Tremor</td>
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<td>Nausea</td>
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Table 2: Severity grade goes from 1 (less severe) to 4 (most severe).

At the end of irradiation there was a clinical response in 27 patients (96.4%), only one patient had no response to RT treatment.

**DISCUSSION**

Brainstem gliomas are a heterogeneous group of tumors that occur predominately in children, have a characteristic appearance in MRI and CT and do not require pathological confirmation: clinical and imaging are considered sufficient for diagnosis;1-4,21 they have a bad prognosis despite initial response to irradiation, which has been the ideal treatment, with a median survival of one year or less.1-3,5,12,21 Radiation dose escalation increases toxicity but does not improve outcome; neither chemotherapy nor hypofractionation1,21-24 have improved therapeutic ratio.

Brainstem gliomas could be diffuse intrinsic pontine gliomas (DIPG) and comprise an entity defined by imaging in- volving pons. Pontine localization was found to be a negative prognostic factor.5 Two more recent studies did not demonstrate similar findings;25,26 these studies included adult patients, possibly confounding results. In our series, we found pontine infiltration in all patients.

Our series of 28 children and adolescents with prolonged treatments involving Nimotuzumab in conjunction with RT showed a median overall survival of 17.3 months and a survival rate at 2 years of 39.7%, exceeding those of earlier reports,22,24,27 and of more recent ones.1,3,5,12,26-34 In a previous case series of patients treated only with RT during the period 1992-2008 in the same Institution (National Oncology and Radiobiology Institute, in Havana), median survival time was 10.0 months and the survival rate at 2 years was 15%. We know that the use of retrospective case series as control groups have limitations, but there are facts that are relevant: all cases were irradiated in the same Institution, so there could not exist center-effects that could bias patient groups.

It is remarkable that in our series there is a preliminary benefit to survival in older ages; it contrasts with reports that young age may predict a better outcome for children with diffuse pontinegliomas.34 Best results were obtained in the group that received 54-57 Gy of RT dosage; increasing RT dosage did not yield better results, consistent with.22,30

The prolonged use of Nimotuzumab for one year or more was well tolerated: adverse events such as alopecia and dermatitis were related to irradiation. Cutaneous rash was also reported but not related; other minor adverse events could be related in part with the clinical evolution of the tumor and the radiation treatment. Nimotuzumab is a humanized monoclonal antibody that recognizes the EGF external domain with intermediate affinity (kd=10-8 )35 that has shown a benefit in addition to RT in different studies.35-37 In children it has been reported with good results and safely associates to RT in CNS and Head and Neck tumors.2,31-44

**CONCLUSION**

The association of focal RT and Nimotuzumab in the treatment of brainstem tumors in children and adolescents was a therapeutic option in order to increase overall survival and support the possibility of new trials with this combination. Radiation dose over 57 Gy did not increase possibilities of survival in our series.

**CONFLICTS OF INTEREST**

No potential conflict of interest exists.

**REFERENCES**


