Low Grade Glioma of Childhood*
Impact of Brain Development*
Strategies for Saving Vision*

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SIOPe International Consortium Low Grade Glioma
LOW GRADE ASTROCYTOMA OF CHILDHOOD
Childhood Low Grade Glioma - ICLGG 1

UK Cohort

- Frontal lobe 2.8%
- Optic nerve only 5.9%
- Chiasma/hypothalamus 24.6% - Combined 30.5%
- Combined 30.5%
- Other supratentorial midline 6.1%
- Cerebellum 31.6%
- Brain stem 9.9%
- Spinal 4.5%
- Occipital lobe 1.7%
- Temporal lobe 5.9%
- Parietal lobe 2.7%
- Ventricles lateral and 3rd ventricle 2.8%
Brain Development

- **Newborn**: brain 25% of adult brain weight
- **2-6 mths**: visual cortex most active
- **6-9 mths**: head growing faster than body, billions of connections
- **9-12 mths**: learning to "read" words, gestures, and expressions
- **12 mths**: hippocampus matures - memory and imitation.
- **12-18 mths**: beginning of complex thinking
- **18-24 mths**: enhanced coordination, cerebellar maturation, cortical connectedness promoting comprehension and pretending
- **24 months**: a hundred trillion synapses, 50% more than adult complement.
- **36 mths**: brain 80% of adult size - subsequent synaptic formation and pruning leading to acceleration of thoughts and actions.
- **Myelinisation**: strengthens connections for language, memory, emotions, attention, planning, sensory integration and coordination of movement.
- **6 - 7yrs**: neuron cell division complete
- **Adolescence**: further myelinisation, cortical maturation, neural re-connection, trophic effects powerful - practice makes perfect
798 patents registered with LGG1

Eligible for analysis (n=639)

Treatment decision after diagnosis

Observation (n=474)

1st Progression (n=108)
- Surgery only (n=15)
- No treatment (n=10)

1st treatment given
- Radiotherapy (n=2)
- Chemotherapy (n=3)

Remained in observation (n=386)
- 2nd Progression (n=1)
- Death (n=3)

Radiotherapy after diagnosis (n=52)
- 1st progression (n=13)
- 2nd treatment given (n=6)
- Death (n=8)

Chemotherapy after diagnosis (n=113)
- 1st progression (n=58)
- 2nd treatment (n=45)
- Death (n=14)

Radiotherapy after observation (n=33)
- 2nd progression (n=14)
- 2nd treatment given (n=4)
- Death (n=4)

Chemotherapy after observation (n=55)
- 2nd Progression (n=22)
- 2nd treatment given (n=16)
- Death (n=5)

Radiotherapy or Chemotherapy treatment (n=253)
- Progression / relapse after treatment (n=107)
- Second treatment given (n=71)
- Death (n=31)
International Consortium Low Grade Glioma Study 1 Strategy
UKCCLG National Cohort n=652 Age< 16 yrs

Age at diagnosis

Age at diagnosis
0
10
20
30
40
50
60
International Consortium Low Grade Glioma Study 1 UKCCLG National Cohort Age-incidence at diagnosis

Cortex / Ventricles  Chiasm / Hypothalamus  Cerebellum

Cerebral hemisphere + lat and 3rd ventricle

Chiasma/hypothalamus

Cerebellum
Kaplan-Meier survival estimates, by agegp

PFS Log rank test p<0.001. No significant difference between 1-3 and 3-5 (p=0.86) or 5-10 and over 10 (p=0.93).
Tumour Site – PFS
Chiasma/Hypothalamus vs non-OPG

Progression-free Survival - Chiasma/hypothalamus vs. Non-OPG

Log-rank test p<0.001

No. at risk (events)
Non-OPG 444 (78) 305 (22) 177 (2) 71 (0) 11 (0) 0
Chiasma/hypothalamus 157 (47) 91 (18) 46 (6) 17 (1) 1 (0) 0
Site and age hypothesis for ongoing tumour growth

- Hypothalamic tumours in under 1 year olds are largest and most aggressive, threatening vision and life.

- As children get older their tumours tend to grow less rapidly.

- Adolescence may be a second risk period for tumour growth before “burnout” occurs.
Meta-Analysis of Systematic Literature Review of Symptoms at Presentation in Childhood CNS Tumours, Ranked by Frequency

* denotes symptoms of raised intracranial pressure

All Children <18 years
n=4171
- headache*
- nausea and vomiting*
- abnormal gait or co-ordination
- papilloedema*
- seizures
- symptoms & signs raised ICP*
- squint
- behavioural change at school
- macrocephaly
- cranial nerve palsies (unspec)
- lethargy
- altered level of conscious
- abnormal eye movements
- hemiplegia
- weight loss
- focal motor weakness
- visual or eye abnormalities
- altered level of consciousness

Children <4 years n=332
- macrocephaly
- nausea and vomiting*
- irritability
- lethargy
- abnormal gait / co-ordination
- weight loss
- clinically apparent hydrocephalus
- seizures
- papilloedema*
- headache*
- unspec. focal neurological signs
- symptoms & signs raised ICP*
- focal motor weakness
- head tilt
- altered level of consciousness
- squint
- abnormal eye movements
- developmental delay
- hemiplegia

Children with NF1 n=301
- reduced visual acuity
- exophthalmia
- optic atrophy
- squint
- headache*
- unspecified symptoms of raised ICP*
- precocious puberty
- abnormal gait or co-ordination difficulties
- voice abnormalities
- developmental delay
- papilloedema*
- reduced visual fields

Wilne et al
Lancet Oncology 2007 8: 685-695
NF1 Associated Optic Pathway Glioma
Severe visual impairment and blindness in children in the UK

THE LANCET • Vol 362 • October 25, 2003 • www.thelancet.com

Childhood sight impairment: a 10-year picture

Table 4 Classification of modifiable causes

<table>
<thead>
<tr>
<th>Category</th>
<th>Children (n=439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entirely unavoidable/untreatable:</td>
<td>178 (69.5%)</td>
</tr>
<tr>
<td>Unknown underlying diagnosis:</td>
<td>9 (3.5%)</td>
</tr>
<tr>
<td>Entirely preventable:</td>
<td>7 (2.7%)</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>2</td>
</tr>
<tr>
<td>ROP</td>
<td>2</td>
</tr>
<tr>
<td>Trauma</td>
<td>2</td>
</tr>
<tr>
<td>NAI</td>
<td>1</td>
</tr>
<tr>
<td>Potentially treatable:</td>
<td>61 (24.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>9</td>
</tr>
<tr>
<td>Cataract</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>9</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>5</td>
</tr>
<tr>
<td>Myopia</td>
<td>5</td>
</tr>
<tr>
<td>Sticklers</td>
<td>3</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>3</td>
</tr>
<tr>
<td>Porencephalic cyst</td>
<td>2</td>
</tr>
<tr>
<td>Retinal haemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>1</td>
</tr>
</tbody>
</table>

Eye (2010) 24, 112–117

Alder Hey Children’s NHS Foundation Trust, Merseyside, UK
Optic Pathway Gliomas in Children with Neurofibromatosis 1: Consensus Statement from the NF1 Optic Pathway Glioma Task Force

Robert Listerick, MD,* David N. Louis, MD,† Roger J. Packer, MD,‡§ and David H. Guttmann, MD, PhD#

Recommendations

Management of the Asymptomatic Child with NF1

1. Screening neuroimaging of asymptomatic children with NF1 for the detection of optic pathway gliomas has not been shown to improve clinical outcome.

2. Serial ophthalmological examinations, particularly in young children with NF1, are very important. We recommend that serial ophthalmological examinations be performed by a pediatric ophthalmologist or neuro-ophthalmologist familiar with NF1. All children who have unexplained ophthalmological abnormalities should also undergo MRI of the head and orbits with contrast enhancement. A suggested schedule for ophthalmological examinations is proposed in Appendix A.
The OPG Classifications

Dodge Classification

PLAN Classification

British Journal of Radiology (2008); 81(970): 761-766
LGG 2004 Non Surgical Treatment Criteria

Visual indications
• Severe preexisting visual disturbance
• Borderline vision in both eyes ( “threat to vision“ )
• Definite history of visual deterioration
• Nystagmus due to impaired vision ( especially in infants up to two years indicative of visual disturbance )

Clinical indication (non visual)
• Diencephalic Syndrome
• Symptomatic metastases

Note: Neuroradiological indication
• The presence of a postoperative residual tumor is not an indication to therapy on its own.
**Chemotherapy for childhood OPG: Visual response**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Schedule</th>
<th>Objective radiological responses (%)</th>
<th>Improving vision (%)</th>
<th>Stable vision</th>
<th>Deteriorating vision</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massimino et al.¹⁶</td>
<td>Cisplatin–etoposide</td>
<td>24 (82.8)</td>
<td>10 (45.5)</td>
<td>7</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Laithier et al.¹⁷</td>
<td>BabyBrain SFOP</td>
<td>51 (60)</td>
<td>2 (3.5)</td>
<td>16</td>
<td>39</td>
<td>57</td>
</tr>
<tr>
<td>Petronio et al.¹¹</td>
<td>Nitrosurea based/TPCV</td>
<td>10 (52.6)</td>
<td>2 (10.5)</td>
<td>14</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Chamberlain and Grafe¹²</td>
<td>Oral etoposide</td>
<td>6 (42.8)</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Janss et al.¹³</td>
<td>Vincristine–actinomycinD</td>
<td>11 (23.9)</td>
<td>5 (18.5)</td>
<td>14</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Silva et al.¹⁴</td>
<td>Carboplatin–vincristine</td>
<td>8 (57.1)</td>
<td>2 (14.3)</td>
<td>12</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Mitchell et al.¹⁵</td>
<td>Carboplatin monthly</td>
<td>1 (8.3)</td>
<td>4 (40)</td>
<td>3</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Dalla Via et al.³</td>
<td>Carboplatin–vincristine</td>
<td>ND</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>25 (14.4)</td>
<td>82 (47%)</td>
<td>67 (38%)</td>
<td></td>
<td>174</td>
</tr>
</tbody>
</table>

*From Moreno et Al. EJC 2009 modified*
Discussion:
Visual outcome after treatment in children with NF1 OPG

• 8/12 symptomatic orbital NF1+ OPG treated with CT
  – 8 Stable vision without any improvement
    (Janice Lasky Zeid et Al. Journal of AAPOS dec, 10, 6, 2006,)

• 15 NF1+ children treated for progressive OPG
  - 9 worse, 5 stable, 1 improved vision
    (Dalla Via et Al, Neuro-Oncology 2007)

• 19 children treated for progressive OPG (57% NF1+)
  – 14 worse, 4 stable, 1 improve vision
    (B. Shofty et Al, PBC 2011)

• 88 evaluable NF1 children treated with CT for OPG
  - 28 % worse, 40 % stable, 32 % improved VA
    (Fisher et Al. Neuro-Oncology 2012)
1 Single optic nerve

Coronal T1, no contrast
8 years old, known NF1
Unilateral OA
Classified 1aL NF+
2 Cisternal segment optic nerve

Axial T1, post contrast
5 years old, known NF1
Classified 1cbR NF+
3 Central chiasm & optic radiation

Axial T2
7 years old, known NF1
Classified 2a 3L NF+
4 Asymmetric chiasm

Coronal and Sagittal T1, post contrast
10 years old, NF1 negative
Prepontine and Hypothalamus
Classified as 2bR H+
5 Multi-site involvement

Axial T1, post contrast and FLAIR
3 years old, Grade 2 Astro on histology
Classified 1cB 2a 3b H+
1. May a new chemotherapy regimen with reduced toxicity (VBL Vs VCR/Carbo) in children with NF1 and OPG result in equal or better outcome (PFS + visual outcome)?

Newly assessed NF1 OPG

Assessment of Indications to treatment (IT)

IT clear:

High risk of visual loss
AND
Expected benefit from CT

R1

VBL only

VCR / CARBO
2. May chemotherapy (VBL) in children with NF1 and “early” OPG prevent visual loss and tumor progression?

Newly assessed NF1 OPG

Assessment of Indications to treatment (IT)

IT unclear:
Low risk of visual loss
AND Expected benefit from CT

R2

VBL only
observation

NF1 OPG SIOP Trial Proposal
The SIOP-NF1 OPG study: Overall design flow

NF1 OPG SIOP Trial Proposal
Introduction of PDE inhibitors (R2 & R3)

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Acknowledgements to:

David A. Walker, Sue V. Picton, Ian Simmons, Astrid Gnekow, Jacques Grill, Amedeo Azizi, Pablo Hernaiz Dreiver, Astrid Sehested, Giorgio Perilongo and the SIOP LGG NF1 working group

Thank you!

NF1 LGG and chemotherapy:
SIOP LGG2004 preliminary results
Tuberous Sclerosis – Giant Cell Astrocytoma
Rapamycin induced response (A/B) / relapse (C) / response (D) in Giant Cell Astrocytoma associated with TS

Franz et al

Ann Neurol 2006:59; 490-498
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Conclusions

• To reduce visual loss due to CNS tumour in childhood?
  - Speed up diagnosis
  - Select patients at greatest risk of visual loss
  - Explore new biologically targeted agents
  - Develop reliable methods for measuring vision in young children