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Glioneuronal tumours in childhood

*Clinical picture, long-term outcome and possible new
treatments*

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Abstract

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Background: Glioneuronal tumours are a subgroup of low-grade tumours of the central nervous system (CNS), often causing epilepsy. Overall survival is excellent, but data regarding long-term seizure outcome and late effects are scarce.

Aims: The overall aim was to gather data about pre- and postsurgical factors of importance and long-term outcomes to improve standards of care. Another aim was to explore the expression of somatostatin receptor (SSTR) subtypes and mTOR pathway markers.

Methods: This thesis, based on four population-based studies with both retrospective and cross-sectional parts, was performed through a long-term follow-up of a Swedish cohort of children with glioneuronal tumours in the Uppsala-Örebro health region. Patients were identified from the National Brain Tumour Registry and the National Epilepsy Surgery Registry. Various methods were used: reviews of hospital medical records, patient interviews, health-related quality of life (HRQoL) assessments with generic (Short Form 36version2) and disease specific (Quality of Life in Epilepsy-31) questionnaires, neuropsychological evaluations with Wechsler Intelligence Scale for Children-IV or Wechsler Adult Intelligence Test-IV and Reys Complex Figure Test and evaluation for possible depression with Hospital Anxiety Depression Scale. Immunohistochemical analyses for SSTR subtypes 1, 2a, 3 and 5 and mTOR pathway components ezrin-radixin-moesin and pS6 were performed on tumour specimens.

Results: Glioneuronal tumours seem to be more frequent than previously reported, accounting for 13.5% of all childhood CNS tumours. They often cause medically refractory epilepsy resulting in cognitive impairment. Neurosurgery was often delayed; mean time from symptom debut to lesionectomy was 4.6 years. Long-term seizure freedom was achieved in 84% of patients who had a gross total resection (GTR) and is important for long-term cognitive restitution, HRQoL, educational and vocational outcomes. SSTR2a and SSTR3 expression was a frequent finding in glioneuronal tumours. Signs of mTOR pathway activation were abundant in ganglioglioma.

Conclusions: A safe GTR should be striven for and considered a first-line treatment. Long-term clinical follow-up should be offered to all patients and for those with an inoperable tumour/tumour remnant causing tumour growth and/or medically refractory epilepsy, somatostatin analogues and/or mTOR inhibitors might represent a therapeutic alternative worth exploring further.

Keywords: Glioneuronal tumour, ganglioglioma, dysembryoplastic neuroepithelial tumour, childhood, cognition, psychosocial, HRQoL, outcome, mTOR pathway, somatostatin receptor

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To Isaac, Leah and Kristina

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I **Ehrstedt C***, Kristiansen I*, Ahlsten G, Casar-Borota O, Dahl M, Libard S, Strömberg B. Clinical characteristics and late effects in CNS tumours of childhood: Do not forget long-term follow-up of the low grade tumours. *European Journal of Paediatric Neurology*. 2016;20(4):580-87. *joint first authorship
- II **Ehrstedt C**, Canto Moreira N, Casar-Borota O, Strömberg B, Ahlsten G. Glioneuronal tumors in childhood – Before and after surgery. A long-term follow-up study. *Epilepsy & Behavior* 2017 Jul;72:82-88.
- III **Ehrstedt C**, Rydell A-M, Gabert Hallsten M, Strömberg B, Ahlsten G. Cognition, health-related quality of life, and mood in children and young adults with a glioneuronal tumor in childhood. *Epilepsy & Behavior* 2018 Jun;83:59-66.
- IV **Ehrstedt C**, Ahlsten G, Strömberg B, Lindskog C, Casar-Borota O. Somatostatin receptor expression and mTOR pathway activation in glioneuronal tumours of childhood. *In manuscript*.

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Abbreviations

AED	Antiepileptic drug
AGG	Anaplastic ganglioglioma
BYI	Beck youth inventory scale
CNS	Central nervous system
DNA	Deoxyribonucleic acid
DNET	Dysembryoplastic neuroepithelial tumour
DIG	Desmoplastic infantile ganglioglioma
ECoG	Electrocorticography
EEG	Electroencephalogram
ERM	Ezrin-radixin-moesin
FCD	Focal cortical dysplasia
FSIQ	Full scale intelligence quotient
GABA	Gamma amino butyric acid
GG	Ganglioglioma
GTR	Gross total resection
HADS	Hospital anxiety depression scale
HE	Haematoxylin-eosin
HRQoL	Health-related quality of life
ILAE	International league against epilepsy
IRS	Immunoreactivity scoring system
LEAT	Long-term epilepsy associated tumour
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NF-1	Neurofibromatosis type 1
NF-2	Neurofibromatosis type 2
OS	Overall survival
PCS	Physical component summary
PGNT	Papillary glioneuronal tumour
PRI	Perceptual reasoning index
PSI	Processing speed index
QOLIE-31	Quality of life in epilepsy-31
RCFT	Reyes complex figure test
SA	Somatostatin analogue
SALUB	Svenska arbetsgruppen för långtids uppföljning efter barn-cancer
SEGA	Sub-ependymal giant cell astrocytoma

SF-10	Short form 10
SF-36v2	Short form 36 version 2
SNESUR	Swedish National Epilepsy Surgery Register
SSTR	Somatostatin receptor
STR	Subtotal resection
TLR	Temporal lobe resection
TRE	Tumour related epilepsy
TSC	Tuberous sclerosis complex
VCI	Verbal comprehension index
WAIS	Wechsler adult intelligence test
WHO	World Health Organization
WISC	Wechsler intelligence scale for children
WMI	Working memory index

Introduction

Childhood central nervous system tumours

Central nervous system (CNS) tumours are, after leukaemia, the second most frequent malignant disease in children and constitute the most common type of solid tumours in childhood. The incidence of brain tumours in Sweden is 4.2/100,000 in children younger than 15 years of age (1), which is comparable to the other Nordic countries (2) and internationally reported figures (3). Primary brain tumours, arising within the CNS, are by far most common. Secondary brain tumours (malignant spread from other malignancies, i.e. lymphoma, leukaemia or other cancers) are rarely seen, unlike in the adult population. Another distinction from the adult population is the tumour location. While a clear majority of the primary CNS tumours in adults are located supratentorially, approximately half of the paediatric CNS tumours arise infratentorially (4-6). A clear majority of the CNS tumours occur sporadic with no known cause, although some tumours can be associated with certain syndromes (i.e. Neurofibromatosis type 1 and 2 (NF-1 and NF-2), Tuberous Sclerosis Complex (TSC), Li-Fraumeni, von Hippel Lindau, Cowden's syndrome, Turcot's syndrome, Gorlin's Syndrome and Constitutional Mismatch Repair Deficiency Syndrome) (7). Regarding environmental factors the only risk factor that has been consistently reported to increase the risk of developing brain tumours is radiation exposure (8). In most reports the most common histologic tumour types are, in descending order, astrocytoma (38-45%), medulloblastoma (12-25%), ependymoma (5-10%), glioneuronal tumours (5-8%) and craniopharyngioma (4-6%) (1, 3, 9-12). Subgrouping of CNS tumours of childhood relies today not only on histopathologic examination, but also on molecular parameters specified in the current World Health Organization (WHO) Classification of Tumours of the Central Nervous System (12-14).

Treatment choices of CNS tumours in childhood depends on different factors: tumour type/subgroup, solitary tumour or signs of dissemination, tumour location and patient age all play an important role. Due to international collaboration there is now often a high consensus regarding treatment regimens for most of the specific tumour subgroups. Most patients receive treatment, the main modalities of which are; surgery, chemotherapy and radiotherapy, either alone or in a combination. In a small proportion of patients, a "wait and see" approach with active expectancy may be justified (i.e. optic gliomas in NF-1

patients, sub-ependymal giant cell astrocytoma (SEGA) in TSC patients or accidentally found tumours when neuroradiology was performed with a different indication). As we continue to refine the tumour classification, we evolve towards a more tailored medicine. “Targeted therapy” aiming at specific genes or proteins is already here (15), and continued development is an obligation to reduce mortality rates as well as morbidity and late effects.

Terminology – “a need for stringency”

Reading through the literature about nomenclature and terminology regarding CNS tumours can sometimes be a confusing experience. There seems to be a need for stringency when using different definitions. The WHO grading scale I-IV can be used as an example. Grade I and II brain tumours are often lumped together under the umbrella “benign” brain tumours (16), because they often display a “benign” biological behaviour. However, the WHO classification does not use this term at all; instead, the WHO’s grading system is a “malignancy scale” ranging across a wide variety of neoplasms (12):

- Grade I – tumours with low proliferative potential and the possibility of cure following surgical resection alone.
- Grade II – tumours that are generally infiltrative in nature and, despite low level of proliferative activity, often recur.
- Grade III – tumours with histological evidence of malignancy, including nuclear atypia and brisk mitotic activity.
- Grade IV – tumours that are cytologically malignant, mitotically active, necrosis-prone and often associated with rapid postoperative disease evolution and a fatal outcome.

It is better to use the WHO grading scale, rather than applying the terms “benign” and “malignant”. If there is a need for lumping brain tumours together a better term is to use “low-grade” tumours for WHO grade I-II and “high-grade” tumours for WHO grade III-IV. Another example of ambiguous use of words is the concept of “gliomas”, which is often used in conjunction with both “astrocytoma” and “low-grade”. The inclusion of histological subgroups in reports on “gliomas” or “low-grade gliomas” can vary greatly (17-20). “Glioma” is a descriptive term, deriving from glial cells, which are “supporting” cells that surround nerve cells in the CNS and help them function (from the Greek word *glia* meaning “glue”). The majority of CNS tumours derives from glial cells of which three types exist that can produce tumours: astrocytes, oligodendrocytes and ependymal cells. Thus, “glioma” is not a neuropathological diagnosis. To improve the stringency and avoid confusion, the use of WHO classification and malignancy scale is recommended.

Outcome – basic concepts and prognostic factors

Outcome can roughly be divided into two major parts: survival and morbidity. Morbidity encompasses a wide range of terms, for example disability, complications, sequelae and late effects. For this thesis the term “late effect” has been used to describe long-term morbidity. Driven by improvements in treatment and early diagnosis, survival curves in childhood cancer have steadily improved during the last decades, an observation especially true for Hodgkin lymphoma, gonadal tumours, leukaemia, renal tumours and non-Hodgkin lymphoma (Figure 1) (21, 22). The same dramatic improvement in survival rates does not apply to CNS tumours. In Sweden, 10-year overall survival rates (OS) in children diagnosed with a primary CNS tumour (1984–2005) have varied between 68% and 76%, although numbers varied greatly across different tumour types. Ten-year OS between 1991–2005 did not differ significantly (21).

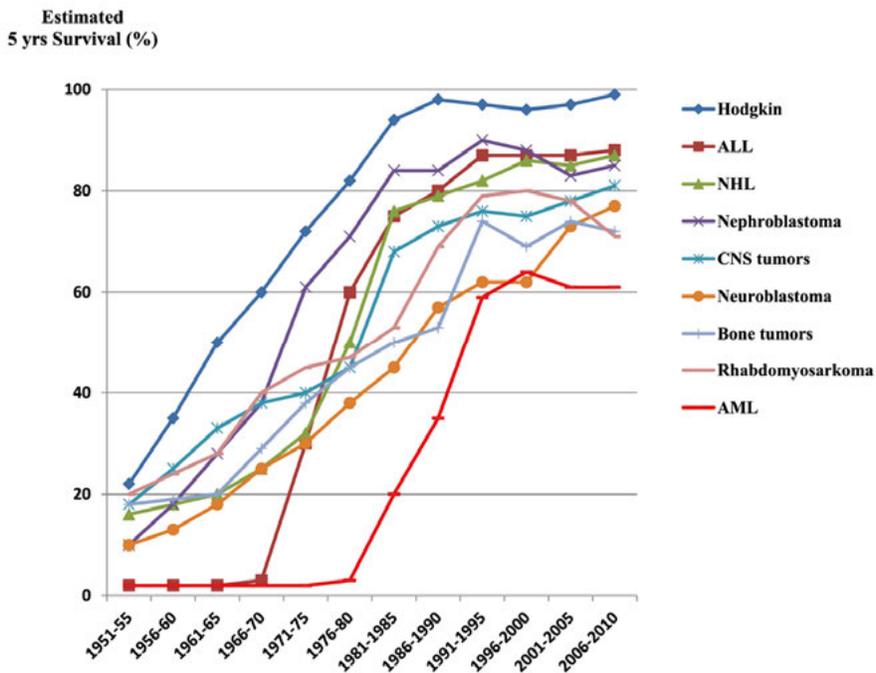


Figure 1 – Five-year estimated OS in childhood cancer in Sweden 1951–2010 (re-produced from Gustafsson et al. (21) with permission).

Initial information to children and adolescents with a newly diagnosed CNS tumour and their caregivers focuses on curing the disease. The only exception is the diffuse intrinsic pontine glioma, carrying a dismal prognosis with a 5-year OS of two per cent (23). However, long-term survivors often “pay a price” – late effects are common. Increasing research interest in this field has been ap-

parent during the last 10–20 years, as indicated by the growing body of literature. Long-term outcome relates to a variety of domains; neurologic and endocrine dysfunction, cognitive deficits and psychosocial outcome, an umbrella term which encompasses health-related quality of life (HRQoL), psychological, social, educational and vocational outcome (24-26), are all of concern. Late effects in these domains are well recognised in the whole group (27, 28), especially among high-grade tumours (WHO grade III-IV) (29-34) but not to the same extent in low-grade tumours (WHO grade I-II) (35). Histological findings of low-grade tumours and favourable survival rates make it easy to miss possible late effects because the patients are considered cured and therefore lost to organised multidisciplinary follow-up. Children with low-grade tumours are considered to be long-term survivors rather than having a life-threatening malignancy (16). Although some studies indicate cognitive difficulties (30, 32, 35-38) there are few studies dealing with the long-term consequences of having had a low-grade brain tumour, with its impact on medical, cognitive, psychosocial functioning and HRQoL (39-44). This indicates a need for multidisciplinary studies to define an optimal medical follow-up and rehabilitation of children with both low- and high-grade CNS tumours and their families.

As mentioned above, one of the most important prognostic outcome factors is tumour subtype. Children and adolescents with low-grade tumours generally do better with respect to different outcome variables than their peers with high-grade tumours. However, prognostic factors also extend beyond tumour subtype; larger tumour size, tumour location in highly eloquent areas (i.e. decreasing the possibility of safe radical surgical resection), signs of dissemination, younger age at diagnosis, and adjuvant treatment with chemotherapy and/or radiotherapy have all been associated with a higher risk of late effects (6, 45). Regarding age as a prognostic factor, there have been discussions about the plasticity versus the vulnerability of the young brain. Research regarding brain tumour survivors, has consistently shown young age to be a risk factor for cognitive late effects (46-49), which is also true for other paediatric neurological disorders (i.e. traumatic brain injury and epilepsy) (50, 51).

CNS tumours and epilepsy

CNS tumours causing epilepsy are far more frequent in the adult than in the paediatric population. This has a dual explanation, partly because a supratentorial tumour location and partly because secondary malignancies in the CNS are more common in adults. However, CNS tumours giving rise to seizures/epilepsy in the paediatric population are not uncommon, with reported numbers varying from 9% to 24% (52-55). In a newly published multi-centre report regarding histopathological findings in brain tissue obtained during ep-

ilepsy surgery, the most common diagnosis in children was focal cortical dysplasia (FCD) 39.3%, followed by tumours (27.2%) and hippocampal sclerosis (15.0%) (56).

Although any tumour affecting the brain has the potential to cause seizures, specific types are more frequently associated with seizures. These are often referred to as long-term epilepsy associated tumours (LEATs), a term that was first coined by the University of Bonn Epilepsy Group (57). Long-term epilepsy associated tumours have been further subdivided into two categories, according to their specific histopathological patterns of differentiation: glioneuronal tumours and glial tumours (58). Glioneuronal tumours, mostly ganglioglioma (GG) and dysembryoplastic neuro-epithelial tumour (DNET), represent by far the most frequently encountered LEATs, but glial tumours such as pilocytic and diffuse astrocytoma, pleomorphic xanthoastrocytoma and oligodendroglioma can also be seen. Thus, the terms LEAT and glioneuronal tumour are not entirely interchangeable. Although LEATs have a malignant potential, they seldom progress or recur. More importantly, they often cause a drug-resistant epilepsy which may give rise to significant late effects.

Mechanisms for tumour related epilepsy

The latest definition of epilepsy was stated in an International League Against Epilepsy (ILAE) official report 2014 (59). In the context of brain tumours, a practical definition is two unprovoked (or reflex) seizures occurring more than 24 hours apart. In 2017 ILAE also provided a revised operational classification of seizure types. In summary, seizures are divided into focal, generalized or unknown onset, with subcategories of motor, non-motor, with retained or impaired awareness for focal seizures (60). Providing a detailed description regarding the pathophysiology of tumour-related epilepsy (TRE) is beyond the scope of this text, however. In summary, two hypotheses have been put forward: the tumour-centric hypothesis and the epileptogenic hypothesis. The former suggests epileptogenicity is derived from the tumour itself, while the latter argues epileptogenicity derives from the peritumoural tissue (19, 61, 62). Regardless of which hypothesis is correct (perhaps both), multiple factors are likely to underpin tumour-associated epileptogenesis: disrupted glutamate homeostasis, weakening of GABAergic inhibitory functioning, alterations in ion channels, blood brain barrier, intercellular connections, brain networks and inflammation have all been put forward as contributing factors (63, 64). However, regarding surgical management of TRE, peritumoural tissue is believed to be of practical importance. Under guidance of electrocorticography (ECoG) and functional intraoperative mapping, a safe surgical resection should aim at removing not only the tumour itself, but also the peritumoural cortex believed to harbour an epileptic focus, thus, leading to a functional surgical neurooncology approach at the interface between neurooncology and epileptology (64).

Epilepsy surgery

Drug-resistant epilepsy (or medical refractory epilepsy) is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drugs (AEDs), in monotherapy or in combination, to achieve sustained seizure freedom (65). In these cases, epilepsy surgery might be a treatment option. The benefits of epilepsy surgery were demonstrated for more than 15 years ago in a randomized controlled trial, where 58% of patients undergoing temporal lobe resections (TLR) were seizure-free 1 year postoperatively, compared to 8% in the medically treated controls (66). This resulted in a practice parameter from the American Academy of Neurology recommending that patients with “disabling complex partial seizures” should be referred to an epilepsy surgery centre when first-line AED treatments have failed (67). This was followed-up with another recommendation for children some years later, with proposed criteria for referral and evaluation for epilepsy surgery (68).

The primary goal of epilepsy surgery is seizure freedom or at least significant seizure reduction. If this can be achieved, secondary gains will follow: discontinuation or lowered doses of AED with fewer side-effects, i.e. improved cognition and quality of life. In the setting of a dedicated epilepsy surgery team involving members from neurology/paediatric neurology, neurosurgery, neurophysiology, neuroradiology, psychology and nuclear medicine, adverse effects can be kept to a minimum. Numerous studies have documented the safety of epilepsy surgery, keeping neurological complications very low. In two recent studies, major surgical complications (defined as complications with lasting sequelae) were seen in 3% of cases, and minor complications (defined as complications that resolve completely within three months) were seen in 8% (69, 70). Temporal lobe resections are the most common form of epilepsy surgery and often involve removal of the hippocampus (medial TLR). Consequently, one of the most common adverse effects is impairment of memory functions linked to temporal lobe functions. Verbal memory decline is a common phenomenon after TLR on the language dominant side (71, 72). Moreover, TLR can affect the posterior part of the visual pathways resulting in visual field defects (i.e. contralateral upper quadrantanopia).

Positive predictive factors for successful surgery and post-operative seizure freedom are positive findings on magnetic resonance imaging (MRI) with discrete lesions, electroencephalographic (EEG) and MRI concordance and GTR (gross total resection) (73, 74). Furthermore, shorter epilepsy duration before surgery, the absence of multiple epileptogenic foci on EEG, low preoperative seizure frequency and absence of generalized seizures have all been associated with better postoperative seizure outcome (57, 75-79).

In Sweden there are six centres with a multidisciplinary epilepsy surgery team (Göteborg, Linköping, Lund, Stockholm, Umeå and Uppsala). A recently performed population-based study based on the Swedish National Epilepsy Surgery Registry (SNESUR) 1990–2004, including 156 patients (103 adults and 53 children) with LEATs (GGs, DNETs or low-grade astrocytoma) or cavernous haemangiomas, predominantly with a temporal lobe location, confirmed the benefits of epilepsy surgery. While surgical complications were low, 77% of the patients were seizure-free two years postoperatively, while another 10% had > 75% seizure reduction. However, late referrals were obvious as indicated by the finding that the mean pre-surgical epilepsy duration for adults and children was 13 years and 5 years respectively (80). Another Swedish study also demonstrates the long-term (mean 7.6 years postoperatively) benefits of epilepsy surgery with respect to seizure outcome. In that study 62% of the operated adults and 50% of the children were seizure free, compared to 14% of the non-operated adults and 38% of the children (81).

Neuronal and mixed neuronal-glial tumours (glioneuronal tumours)

Classification of glioneuronal tumours

During the last century CNS tumour diagnosis and classification has been based primarily on light microscopic features in haematoxylin-eosin (HE) stained sections, immunohistochemical expression of lineage associated proteins (for example glial fibrillary acidic filament, neurofilament, synaptophysin and S-100) and ultrastructural characterization (13). In today's "genomic era" molecular parameters have been incorporated into the classification of CNS tumour entities. Thus, during the last decade there has been a vast expansion regarding the classification of CNS tumours. Neuronal and mixed neuronal-glial tumours, more often called glioneuronal tumours, are thought to arise from neuroepithelial cells and are considered to be developmental tumours. Common to these tumours is the fact that they are composed of cells with neuronal differentiation, sometimes accompanied by a second cellular component with a glial phenotype. A possibility of these tumours deriving from a common single neuroglial precursor cell exists (82). Although the diagnosis of glioneuronal tumours still relies on microscopy to a major extent, new subtypes have also emerged in this group. According to the latest WHO classification from 2016 (12), this tumour entity now comprises the following subgroups:

- Dysembryoplastic neuroepithelial tumour (DNET)
- Gangliocytoma
- Ganglioglioma (GG)

- Anaplastic ganglioglioma (AGG)
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
- Desmoplastic infantile astrocytoma and ganglioglioma (DIG)
- Papillary glioneuronal tumour (PGNT)
- Rosette-forming glioneuronal tumour
- Diffuse leptomeningeal glioneuronal tumour
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma
- Paraganglioglioma

Despite refinements and improvements regarding this sub-classification, there still seem to be difficulties in classifying these tumours. Although most publications on epilepsy-associated brain tumours specify GGs as the most frequent tumour type followed by DNETs (16, 57, 83), the frequency of reported GGs and DNETs varies. Numbers in different series ranging from 6% to 49% (GG) and 7% to 80% (DNET) suggest poor inter-observer correlation and that neuropathologists are struggling with this distinction (58). An example of the neuroradiological and the histopathological features of the two most common subgroups (i.e. GG and DNET) is demonstrated in Figure 2 (panel a-d).

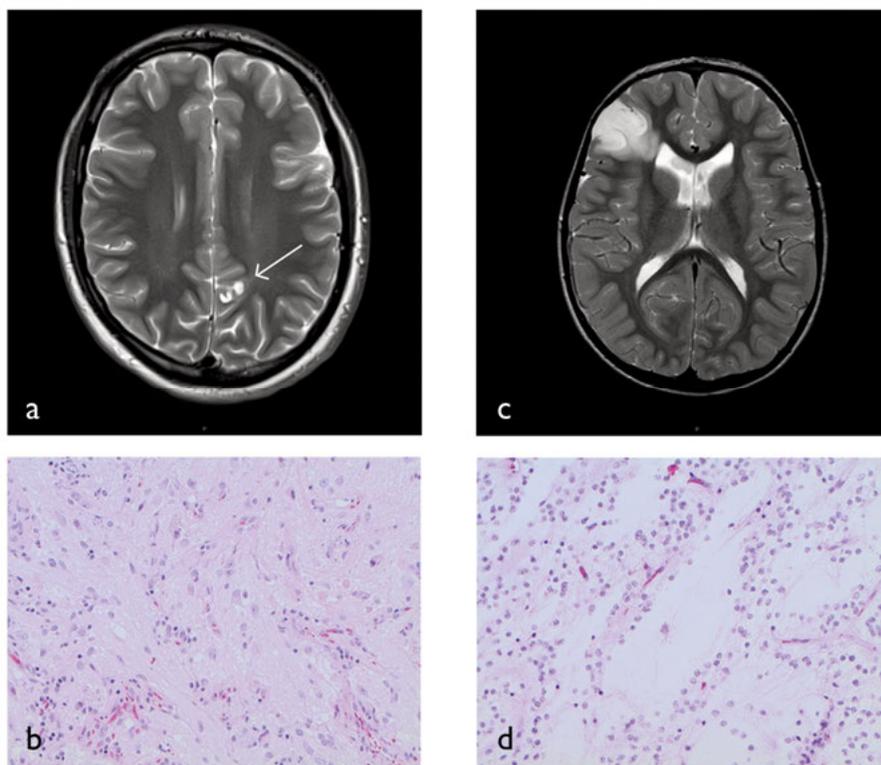


Figure 2 (panel a-d) – (a) T2 weighted MRI image of a ganglioglioma with a left parasagittal location (white arrow) with (b) corresponding microphotograph demonstrating a biphasic tumour area composed of dysplastic neurons and interspersed neoplastic glial cells. HE-staining, magnification x 200. (c) T2 weighted MRI image of a DNET with a right frontal location with (d) corresponding microphotograph demonstrating oligodendrocyte-like cells in a mucoid matrix with a single floating neuron. HE-staining, magnification x 200. Both patients had medically refractory epilepsy.

Most glioneuronal tumours are well differentiated corresponding histologically to WHO grade I with a very low risk of malignant transformation. However, both the glial and neuronal compartment of these tumours can be true neoplastic components and cause tumour progression (84). The high-grade variant of GG, i.e. AGG, corresponds to WHO grade III and the rates are low. In a large study of 184 patients with supratentorial gangliogliomas, they accounted only for 1% (85). In cases of malignant transformation and tumour progression, this has often been coupled with hTERT promoter mutation (61%), p53 accumulation (39%), ATRX loss (17%) and p.K27M H3F3A mutation (17%) (82). BRAFV600E mutations have been observed with both immunostaining and by DNA sequencing (gold standard) in GG WHO grade I

and AGG WHO grade III (82, 86-88). Although the presence of BRAFV600E mutation does not seem to be of prognostic importance, it may be of practical importance due to development of BRAF inhibitors (i.e. vemurafenib and dabrafenib) as a potential treatment alternative (86).

Epidemiology

Glioneuronal tumours, GG and DNET, are most often encountered during the first two to three decades of life (12, 89-91). Mean age at diagnosis varies between 9.5 and 10.3 years in two major surveys including only children (12). Glioneuronal tumours have a male preponderance. In children and adolescents younger than 18 years of age, these tumour types represent between 5–8% of the total CNS tumours (1, 3, 9-12).

Clinical characteristics and treatment

Glioneuronal tumours can be encountered throughout the CNS; supratentorial, infratentorial, brainstem and spinal locations have all been observed. As in all CNS tumours, symptoms may vary depending on tumour size and location (92), but with a supratentorial and especially temporal predilection these tumours often give rise to focal seizures with impairment of awareness. Anaplastic GG seem to have a mid-line location more frequently, and thus less seizures, although a temporal location also can be observed in these cases (82). Debut of symptoms often occurs in school age. Neuroradiological diagnosis is often delayed (93), whether this is caused by the patient's or the doctor's delay is difficult to tell, but it is probably a combination of both. Given their high differentiation they seldom malignify. First-line treatment is therefore primarily symptomatic, i.e. achieving seizure freedom or reduction through AEDs. However, AED treatment often fails to be a sustainable solution, as many develop medically refractory epilepsy (94). Indications for neurosurgical removal today are: 1) medically refractory epilepsy, 2) tumour progression as indicated by subsequent MRIs or 3) a combination of these. Thus, today's standards of care are often influenced by a "wait and see" approach resulting in a prolonged time span from neuroradiological diagnosis to surgery. Intuitively, this would affect patients' cognitive performance and psychosocial outcome including quality of life in a short time perspective. However, whether it affects long-term outcomes remains to be proven. Aggressive neuro-oncological treatment with radiotherapy and/or chemotherapy is reserved for rare cases with anaplastic features or malignant transformation resulting in progressive disease, which occurs very seldom (95). Thus, these treatment modalities do not affect outcome measures on a group level.

Outcome

Given that glioneuronal tumours most often represent WHO grade I-II, long-term outcome with respect to survival is excellent (1, 85, 96). In paediatric and adult series rates of 5-year OS have been reported with numbers of 97% and 86–95% respectively (97). Tumour recurrence after GTR is seldom seen (75). In the rare case of anaplastic disease, the prognosis is clearly worse, with 5-year OS numbers between 53% to 88% (85, 96, 98, 99). Despite excellent survival rates without the need of adjuvant therapy with chemotherapy and/or radiotherapy, there is a non-negligible risk that these tumours may cause considerable morbidity. This is partly because an uncontrolled TRE and partly because ongoing AED treatment, which is often given in high doses and sometimes as polypharmacy, can result in undesirable side effects. It is a well-known fact that epilepsy, irrespective of aetiology, and AED might cause numerous problems such as cognitive impairment, psychiatric comorbidity, driving restrictions, fear, social stigma and discrimination, which all may have a negative impact on psychosocial outcome and quality of life (100, 101). Uncontrolled TRE has been linked to cognitive deterioration and a negative impact on quality-of-life in adults with low-grade gliomas (102, 103). Studies of social outcome following temporal lobe surgery for intractable epilepsy during childhood have demonstrated a benefit from long-term seizure freedom (104). Regarding glioneuronal tumours there is a lack of long-term data to provide insight into cognitive function and psychosocial outcome, including quality of life (105-107).

Lesionectomy has been proven to be a safe and in most cases effective method to alleviate or reduce seizures when AEDs fail, especially when GTR is achieved (44, 75, 79, 94). Per- or/and postoperative neurosurgical complications can often be kept to a minimum if careful multidisciplinary pre-operative epilepsy and/or tumour surgery planning has been applied to avoid highly eloquent cortex. Post-operative neurological sequelae affecting speech, vision or motor function are seldom seen.

Today, there is an abundance of paediatric studies reporting on excellent seizure outcome, but most of them have a relatively short follow-up time of less than five years, describing seizure control in 62% to 95% (76, 105, 108-114). Declining seizure control rates with relapses over time are described, mainly correlated to incomplete resections and occurring shortly after surgery (44, 79). However, there are insufficient data covering the aspect of long-term seizure control and possible risk of late seizure recurrences. Bearing this in mind, and the fact that some studies report better outcomes in cognitive and psychosocial domains if seizure freedom is achieved (44, 104), there is a non-negligible risk that these children and adolescents, with supposedly favourable outcomes, are considered cured and lost to long-term follow-up. Gathering long-

term data is important before such an assumption can be adopted. Consequently, more long-term follow-ups are needed.

Association to focal cortical dysplasia

Focal cortical dysplasias are localized malformations of cerebral cortex frequently associated with epilepsy in both children and adults (115-117). During the last few decades different classifications of FCD have been used. In 2011 the ILAE Task Force proposed a new three-tiered classification system, as well as defining the terminology of “dual” and “double” pathology, a terminology that has been ambiguously used in clinical and histopathologic practice (118). The new three-tiered classification system comprises the following subgroups:

- FCD type I (refers to isolated lesions)
 - FCD type Ia with radial dyslamination of the neocortex
 - FCD type Ib with tangential dyslamination of the neocortex
- FCD type II (refers to isolated lesions with cytological abnormalities)
 - FCD type IIa with cortical dyslamination and dysmorphic neurons
 - FCD type IIb with cortical dyslamination and dysmorphic neurons and balloon cells
- FCD type III (refers to cortical lamination abnormalities + another principal lesion)
 - FCD type IIIa with cortical lamination abnormalities + hippocampal sclerosis
 - FCD type IIIb with cortical lamination abnormalities + tumour (i.e. LEAT)
 - FCD type IIIc with cortical lamination abnormalities + vascular malformation
 - FCD type III d with cortical lamination abnormalities + another acquired lesion during early life (i.e. traumatic brain injury, glial scarring after bleeding, ischemic injury, inflammation or infection)

“Dual” pathology refers only to patients with FCD type IIa or IIb + hippocampal sclerosis, while “double” pathology refers only to patients with FCD type IIa or IIb + another principal lesion (i.e. glioneuronal tumour). A significant proportion of glioneuronal tumours, especially GG and DNET, have been associated with FCD; figures between 30–80% have been reported in studies including adult patients prior to 2011 (119). Paediatric studies investigating the association between glioneuronal tumours and FCD using the new classification system are lacking.

Prognostic factors

Prognostic factors studied up to the present relate mainly to seizure outcome. Gross total resection and short epilepsy duration (≤ 1 -year duration of epilepsy) have been reported as significant predictors of seizure freedom (75, 79). Mesial temporal tumour location has also been associated with favourable seizure outcome. Moreover, extended resection of temporal lobe tumours, with hippocampectomy and/or corticectomy, has conferred additional benefit, suggesting that other pathologies (i.e. cortical dysgenesis, gliosis and hippocampal sclerosis) might contribute to ictogenicity in these lesions (120). Most studies do not report the coincidence of other potentially epileptogenic lesions, nor “double” pathology (i.e. FCD type IIa or IIb), or whether this affects seizure outcome (79). Seizure outcomes have not differed significantly between children and adults, patients with temporal lobe versus extratemporal tumours, pathologic diagnosis (GG versus DNET), medically controlled versus refractory seizures or the intraoperative use of ECoG (79).

Although short epilepsy duration has been reported as a significant predictor of seizure freedom, timing of surgery still is a matter of debate (44, 75, 79, 94, 120, 121). Linking seizure freedom to better outcomes regarding psychosocial, cognitive function and quality of life may be an important factor supporting the need for early surgical intervention.

mTOR pathway activation and somatostatin receptor expression

A small number of patients will have an inoperable tumour or tumour remnant, causing medically refractory epilepsy and/or tumour growth, supporting the search for alternative treatment regimens. The mammalian target of rapamycin (mTOR) serves as a central regulator of cell metabolism, growth, proliferation and survival. mTOR pathway activation has been observed in tumour formation (122). mTOR inhibitors, rapamycin and its analogues (“rapalogues”), have demonstrated seizure-reducing and anti-tumour effects in patients with TSC and SEGA (123). There is some evidence in the literature that the mTOR pathway is activated in GGs (124, 125).

A presence of somatostatin receptors (SSTRs) has been demonstrated in some subgroups of CNS tumours, for example meningiomas and pituitary adenomas (126-128). Somatostatin, an endogenous neuropeptide with a very short half-life, binds to five different subtypes of plasma membrane somatostatin receptors (SSTR 1-5) (129) and has been suggested to possess anti-epileptic properties in animal models (129, 130). Synthetic somatostatin analogues (SAs, i.e. octreotide, lanreotide and pasireotide), with much longer half-lives, have anti-tumour properties in several tumours (131-133). Moreover, a combination of the mTOR inhibitor rapamycin and octreotide has been found to have

additive anti-tumour effect in pituitary tumour cells and meningiomas (134, 135). In some experimental models of status epilepticus, SAs evinced seizure reducing effects (136).

Studies regarding SSTR expression in paediatric glioneuronal tumours do not seem to exist, and for mTOR pathway activation, available data mostly rely on adult cases. There are many new AEDs and, although better tolerated, it is not known whether they are more effective than the old ones. Therefore, it would be of interest to investigate if mTOR pathway activation and SSTR expression are present in paediatric glioneuronal tumours. If so, mTOR inhibitors, either alone or in combination with an SA could possess potential therapeutic properties, i.e. seizure reducing and/or anti-tumour effect.

Aims of the thesis

In this thesis we have performed a thorough long-term follow-up of a Swedish cohort of children with glioneuronal tumours in the Uppsala-Örebro health region. The overall aim of this thesis was to gather data about pre- and postsurgical factors of importance and long-term outcomes to improve our standards of care and pre-operative counselling to patients and caregivers.

The specific study aims were:

- Study I
To describe the clinical characteristics, investigate the frequency of neurological, endocrinological and neuropsychological late effects and to investigate whether cognitive difficulties have been met by pedagogic interventions in school in children with CNS tumours.
- Study II
To give a detailed description of a cohort of children with glioneuronal tumours regarding clinical characteristics and pre-surgical findings, including “double” pathology. Moreover, we wanted to study long-term outcome with regards to; seizure freedom, neurologic late effects, educational and vocational outcome.
- Study III
To study long-term cognitive outcome, HRQoL and frequency of possible psychiatric symptoms in children and young adults diagnosed with a glioneuronal tumour in childhood.
- Study IV
To explore the expression of the different subtypes of SSTRs and investigate expression of mTOR pathway markers in glioneuronal tumours of childhood.

Patients and methods

Study I

Design

A retrospective population-based single-centre study.

Patients and methods

This study was performed at Uppsala University Children's Hospital, Sweden, a tertiary referral centre for children with CNS tumours. Patient data were retrieved from the local treatment centre, the National Brain Tumour Registry and the SNESUR. All 193 patients with a CNS tumour (age 0–17.99 years) diagnosed during a 12-year period (1995–2006) were included. All patients had a follow-up time ≥ 5 year. Hospital medical records were retrieved and scrutinized from paediatric, neuropaediatric, neurooncology, neurosurgery and neuropathology departments as well as neuropsychology records including pre- and postoperative neuropsychological assessments. Re-evaluation of the neuropathological diagnosis based on identification of histopathological criteria and immunohistochemical data, according to the current WHO Classification of Tumours of the CNS (14) was performed by two experienced neuropathologists (OCB and SL) in all eligible cases (i.e. biopsy undertaken). Original HE and immunohistochemically stained sections were re-evaluated. In some cases, additional immunohistochemical analyses were performed to fulfil diagnostic requirements as defined in the WHO classification.

Study II

Design

A retrospective population-based single-centre study with a cross-sectional long-term follow-up part.

Patients and methods

During a 15-year period (1995–2009) all patients (age 0–17.99 years) with a glioneuronal brain tumour diagnosed and treated at Uppsala University Children's Hospital were identified from the local treatment centre, National Brain Tumour Registry and the SNESUR. Hospital medical records were reviewed and neuroradiological and neuropathological findings were re-evaluated. A cross-sectional long-term follow-up part, including an interview, neurologic examination and EEG, was accomplished in patients accepting participation.

A total of 30 patients were identified. Two patients were excluded (one with a severe cerebral palsy with gross motor function classification system level IV and one patient with a progressive glioneuronal tumour in the medulla oblongata/pons who died despite intensive chemotherapy). A total of 25 out of 28 eligible patients (89%) accepted participation in the cross-sectional part of the study. All patients had a follow-up time of more than five years (mean: 12.1; range: 5.0–19.3).

An experienced paediatric neurologist (CE) performed the interview and neurologic examination. The original neuropathological slides were re-evaluated by two neuropathologists for study I and the tumours classified according to the current WHO Classification of Tumours of the CNS (14). For the present study, a single senior neuropathologist (OCB) assessed structural changes in cortical brain tissue outside the tumour. Additional immunohistochemical analysis with anti-Neu N antibody visualizing neurons was performed to assess architectural changes in cortex. Antibodies towards phosphorylated neurofilament protein (clone SMI31) and non-phosphorylated neurofilament protein (clone SMI32) were used to assess the presence of dysmorphic neurons in the cases where a satisfactory amount of cortical tissue was present and where cortical changes were suspected based on standard HE-staining. Re-evaluation of pre- and postoperative neuroradiological examinations with MRI was performed by an experienced neuroradiologist (NCM). Evaluation of the EEGs was performed by experienced neurophysiologists.

Study III

Design

A retrospective population-based single-centre study with a cross-sectional long-term follow-up part.

Patients and methods

Study III deals with the same patient cohort as study II. A total of 24 out of 28 eligible patients (86%) accepted participation in the cross-sectional part of the study. All patients had a follow-up time of more than five years (mean: 12.1; range: 5.0–19.3). A cognitive evaluation was performed by a senior neuropsychologist (MGH) with the Wechsler Intelligence Scale for Children (WISC-IV) or Wechsler Adult Intelligence Scale (WAIS-IV) and the Rey's Complex Figure Test (RCFT). These data were compared with results from historical neuropsychological tests (WISC-III and RCFT), performed before surgery and two years post-operatively. Generic and disease specific quality of life assessments were made with Short Form 36 version 2 (SF-36v2), Short Form 10 (SF-10) and Quality of Life in Epilepsy 31 (QOLIE-31). Hospital Anxiety and Depression Scale (HADS), Becks Youth Inventory Scales (BYI) and Rosenberg Self Esteem Scale were used to screen for depression, anxiety and self-esteem problems.

Study IV

Design

A cross sectional population-based cohort study.

Material and methods

All patients (age 0–17.99 years) with a glioneuronal brain tumour diagnosed and treated at Uppsala University Children's Hospital during a 22-year period (1995–2016) were identified from the National Brain Tumour Registry and the SNESUR. A total of 37 patients with a neuropathological confirmed diagnosis of a glioneuronal tumour were found. Four patients were excluded due to insufficient tumour material for immunohistochemical analyses of SSTRs and mTOR-pathway markers. Thus, 33 tumours were eligible for the study and re-classified according to the latest WHO classification of tumours of the central nervous system (12).

We used paraffin blocks cut in 4 μ m thick sections for immunohistochemical staining. Immunohistochemical analysis of SSTRs was performed using a

Dako Autostainer Plus and Dako EnVision FLEX system (K5007; Dako, Glostrup, Denmark). The following primary monoclonal antibodies against SSTRs were used: anti-SSTR1 (clone UMB-7, catalogue number ab137083, dilution 1:100), anti-SSTR2a (clone UMB-1, catalogue number ab134152, dilution 1:1000), anti-SSTR3 (clone UMB-5, catalogue number ab137026, dilution 1:4000), and anti-SSTR5 (clone UMB-4, catalogue number ab109495, dilution 1:750). Neuroendocrine cells in pancreatic islets of Langerhans were used as positive controls.

Immunohistochemical analysis of mTOR pathway markers was performed using Autostainer 480® instruments (Lab Vision, Fremont, CA) and LabVision UltraVision LP detection system (TL-125-HD, Thermo Fisher Scientific, Waltham, MA). Primary antibodies were anti-p-S6, Ser235/236, (product 4858, 1:500) and anti-Ezrin-Radixin-Moesin ((ERM), product 3142, 1:100) both rabbit monoclonal antibodies (Cell Signalling Technology, Danvers, MA). A tumour sample from a TSC patient with SEGA was used as positive control.

The immunohistochemical expression of SSTRs and mTOR pathway markers was assessed and quantified semi-quantitatively using the immunoreactivity scoring system (IRS); the 0–12 IRS score is the product of the proportion of immunoreactive cells (0=0%; 1=1–10%; 2=11–50%; 3=51–80%; 4>80%) and the staining intensity (0=no staining; 1=weak; 2=moderate; 3=strong). For statistical purposes, IRS scores were divided into three groups; absent/low (IRS 0–3), intermediate (IRS 4–8) and high (IRS 9–12). An IRS score of ≥ 4 was determined to be significant.

Ethical considerations

All studies in this thesis were approved by the Regional Ethical Review Board in Uppsala (EPN Uppsala Log. No. 2010/229, 2010/229/2 and 2014/245).

Statistical methods

Statistical analysis was performed using the SPSS statistical program. Non-parametric tests were used due to small sample sizes and non-normal distribution of data. Categorical or dichotomized variables were analysed with Fisher's exact test. For continuous variables univariate analyses with the Mann–Whitney U test were performed. When comparing cognitive and HRQoL data with reference/norm, one-sample Wilcoxon signed-rank test was used, while longitudinal cognitive data were analysed with the related Wilcoxon signed-rank test. In between group comparisons of seizure-free patients

and patients with remaining epilepsy with respect to cognitive and HRQoL data, were analysed with the independent samples Mann–Whitney U test. Kaplan–Meier curves were used to illustrate postoperative seizure outcome over time, and a log rank test was used when comparing extent of surgery to seizure outcome. Correlation between age at epilepsy onset and cognitive outcome was investigated with Spearman’s rho. All statistical tests were 2-tailed, and the level of significance was set at $p < 0.05$.

Results and discussion

Clinical characteristics and late effects in children with CNS tumours (study I)

The mean age at diagnosis was 9.0 years (median 9.8 years), and there was a male dominance with a male/female ratio of 1.4/1. At presentation (i.e. neuroradiological diagnosis) most patients (87%) had a medical history without any previous disease and 97% evinced normal psychomotor development. Certain syndromes coupled with an increased risk of having a CNS tumour were seen in 5%, mostly NF-1. Regarding tumour classification, three large subgroups could be identified: astrocytic, embryonal and neuronal and mixed neuronal-glial tumours (i.e. glioneuronal tumours). The frequency of glioneuronal tumours, 13.5%, is considerably higher than previously reported, making this tumour type the third most common CNS tumour after astrocytic and embryonal tumours. By combining data from the National Brain Tumour Registry together with the SNESUR, we are confident that this finding is robust. A detailed distribution of tumour diagnoses in the cohort, according to the WHO classification (14), after neuropathological re-evaluation is shown in the following table.

Table – The distribution of tumour diagnoses according to the WHO classification from 2007 after neuropathological re-evaluation.

WHO classification	Number	Per cent (%)
Astrocytic tumours	62	32.1
Low-grade astrocytoma	47	24.3
High-grade astrocytoma	15	7.8
Embryonal tumours	27	14
Medulloblastoma	22	11.4
Supratentorial primitive neuroectodermal tumour	5	2.6
Neuronal and mixed neuronal-glial tumours	26	13.5
Ganglioglioma	22	11.4
Dysembryoplastic neuroepithelial tumour (DNET)	4	2.1
Tumours of the sellar region	15	7.8
Craniopharyngioma	10	5.2
Pituitary adenoma	5	2.6
Ependymal tumours	11	5.7
Germ cell tumours	9	4.7
Tumours of the pineal region	6	3.1
Tumours of the meninges	6	3.1
Oligodendroglial tumours	5	2.6
Oligoastrocytic tumours	4	2.1
Tumours of cranial and paraspinal nerves	4	2.1
Choroid plexus tumours	2	1.0
Other neuroepithelial tumours	1	0.5
Unclassified	15	7.8
Total	193	

The location of CNS tumours in children is sometimes described as predominantly infratentorial (37). Our study argues against this description. Tumour location was supratentorial in 52%, infratentorial in 38%, and spinal cord in 7%, and 3% were found in the cranial nerves or had multiple locations. However, in line with other reports (6, 7), age had an impact on tumour location. An infratentorial location was seen more frequent in younger age groups (3–10.99 years) with astrocytic and embryonal tumours dominating, while a supratentorial location dominated in older age groups (11–17.99 years) with glioneuronal tumours as the most common type.

There was a wide variation in presenting symptoms at tumour diagnosis, reflected partly by the variable tumour location, but also by the tumour type and age of the patients. The most common debut symptoms were headache, nausea and vomiting (56%) related to increased intracranial pressure, followed by cranial nerve disturbances (35%, mainly affecting vision), motor symptoms (29%) and seizures (18%). Fifty-five per cent had duration of symptoms less than three months before neuroradiological diagnosis. However, there were also 26% with duration of symptoms more than six months. Particularly patients with sellar and glioneuronal tumours tended to have a delayed diagnosis, more than six months from start of symptoms until neuroradiological diagnosis in 54% and 53% respectively.

The 5-year OS rate was 77% (n=149). The lowest survival rate was seen among embryonal tumours, with 59% 5-year OS. Among the astrocytic tumours 5-year OS was 71% (7% among high-grade astrocytoma and 91% in low-grade astrocytoma). Glioneuronal tumours had 100% 5-year OS.

The frequency of late effects in all CNS tumours was recorded in long-term survivors, i.e. living ≥ 5 years after diagnosis (Figure 3). Although a retrospective study, study I pointed out high frequencies of medical late effects in surviving children. Neurological late effects were seen in 81% and endocrinological in 26% of the patients. The most common neurological late effects included difficulties with visual and motor functions followed by impaired hearing and epilepsy. Growth hormone deficiency, isolated or in combination with other hormone deficiencies, was the most common endocrinological late effect. Cognitive late effects were also a common finding. Of the patients who underwent postoperative neuropsychological testing within 24 months after treatment, 68% (50/74) had some form of abnormality in the test results. Among those with astrocytic and embryonal tumours, abnormal results were seen in 53% (9/17) and 79% (11/14), respectively. More comprehensive cognitive data were retrieved in the glioneuronal group where 54% (14/26) of the patients had a neuropsychological assessment with WISC postoperatively. Mean scores for all the different domains, verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), processing speed index (PSI) including FSIQ (full scale intelligence quotient), were below the mean for the relevant age and sex normative group, although the range was wide. Compared to a mean score of 100, none of the indices was significantly lower, although PSI clearly tended towards this ($p = 0.056$).

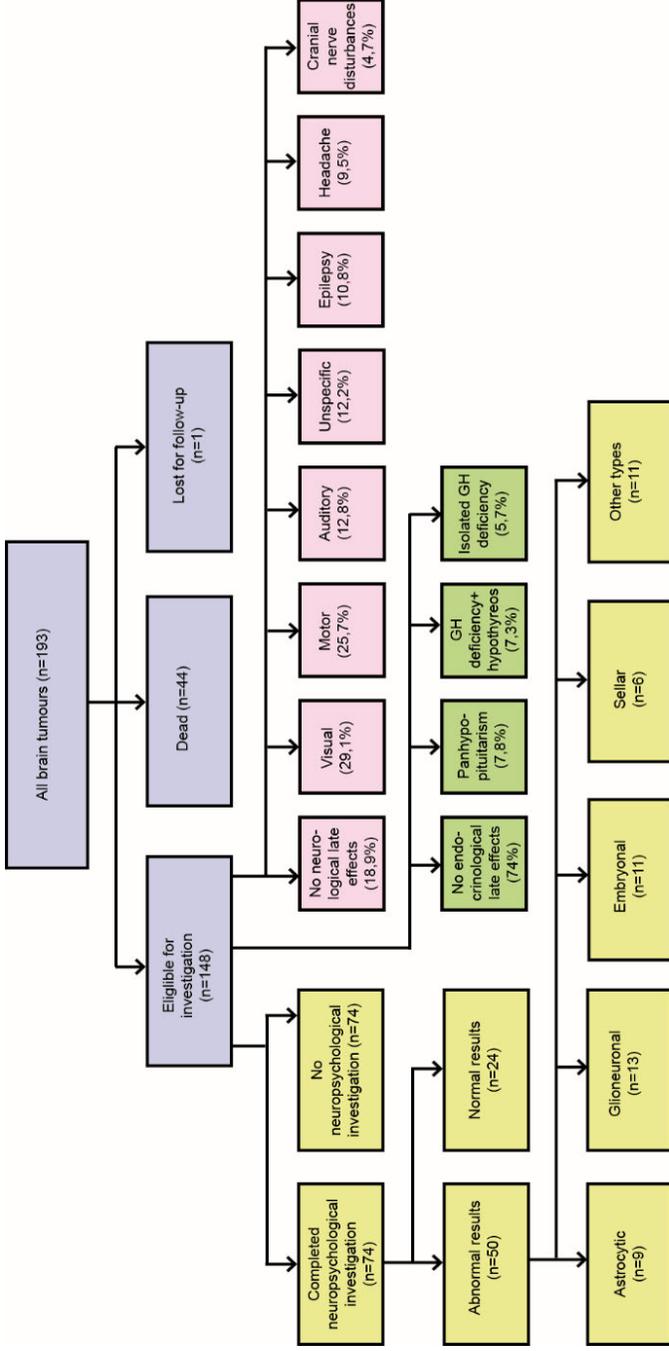


Figure 3 – Medical late effects and results of neuropsychological investigations for patients with 5-year OS. More than one neurological late effect is possible for each patient.

Parental information reported learning difficulties in 48% of the patients. Among those with glioneuronal, low-grade astrocytoma and embryonal tumours, these numbers were 58%, 41% and 88% respectively.

It is important to note that the high number of cognitive late effects and reported learning difficulties do not necessarily reflect the situation in school. Ninety-six per cent were enrolled in mainstream schools; of these, 30% received remedial education. Three per cent were enrolled in classes for children with cognitive disabilities. In the embryonal group 56% received remedial education and 19% were enrolled in classes for children with cognitive disabilities. Twenty-three per cent of those with glioneuronal tumours received remedial education (n=5) or were enrolled in special schools (n=1) whereas 33% of those with astrocytic tumours received remedial education. This indicates that there are unmet needs in schools.

Importantly, the above-mentioned medical and cognitive late effects were not only restricted to patients with high-grade tumours but were also a common finding in children with low-grade tumours, whom in many cases had not received any adjuvant chemo- and/or radiation therapy. Data from postoperative cognitive and neuropsychological assessments had several limitations. Only 50% (74/148) of the patients completed a neuropsychological assessment. Furthermore, there was a heterogeneity regarding neuropsychological tests being used and time point of assessments.

Clinical characteristics in children with glioneuronal tumours (studies II and III)

Most of the patients included had normal preoperative psychomotor development. The male-female (M:F) ratio was 1.8:1. A clear majority of the patients with glioneuronal tumours presented with seizures as the first debut symptom (93%). Focal seizures with impairment of awareness were the most common seizure type, either alone or in combination with focal seizures without impairment of awareness or focal evolving to bilateral convulsive seizures. Symptoms associated with elevated intracranial pressure (headache, nausea and/or vomiting) were present in 18%. Mean age at symptom debut was 7.2 years (range 0.02–17.08). Fifty per cent had symptom debut before seven, 79% before 13 years of age. A neuroradiological diagnosis of a glioneuronal tumour was made late in many cases with a mean duration from symptom debut until diagnosis of 2.8 years. All tumours were located supratentorially with a temporal lobe location in approximately two thirds of the patients. Almost all patients had tried AED preoperatively (86%), and 50% had medically refractory epilepsy preoperatively, defined as at least monthly seizures despite treatment with AEDs.

Neurosurgery was performed in all 28 cases, and the main indications were: medically refractory epilepsy combined with a slight tumour progression on subsequent MRIs (43%), medically refractory epilepsy without tumour progression (36%) and tumour progression alone (21%). The mean duration from neuroradiological diagnosis until surgery was 1.5 years if tumour progression contributed to the decision of surgery, compared to 2.1 years if medically refractory epilepsy alone resulted in surgery. Gross total resection was achieved in most patients, 68%. Among the rest subtotal resection (STR) and stereotactic biopsy was performed in 25% and 7%, respectively. A tumour location in proximity to highly eloquent cortex made GTR impossible in 21%. Neurosurgery seemed to be safe, as a minor complication occurred in only one patient, a self-limiting intracranial bleeding with slight oedema causing headache, treated conservatively with rest and steroids.

Study II confirms some previous findings regarding glioneuronal tumours, i.e. seizures as the main debut symptom (most often focal with impairment of awareness), supratentorial location with a temporal predilection and a male preponderance. More importantly, a neuroradiological diagnosis is often delayed. Adding a “wait and see” approach after neuroradiological diagnosis resulted in a mean time from symptom debut to lesionectomy of 4.6 years, despite the finding that approximately 50% of the patients had medically refractory epilepsy. Unpublished data correlating time of epilepsy debut (1995–2016) with epilepsy duration before neurosurgical intervention demonstrated significantly shorter epilepsy duration for patients operated on more recently ($r=-0.46$; $p=0.005$). However, a few of the earliest diagnosed patients in our cohort seemed to be outliers with exceptionally long epilepsy duration before surgery was performed. Excluding these patients from the statistical analysis led to non-significant results. Thus, it would be important to see if this trend holds true in a larger nationwide cohort, since shortening the epilepsy duration is important for long-term outcome (79).

Tumour relapse never occurred if GTR was performed, but tumour progression was seen in 25% (2/8) in the STR/biopsy group. The length of postoperative neuroradiological surveillance was 5.0 years (range 0.3–16.3), but it was highly dependent on extent of surgery and seizure outcome. A clear tendency to longer postoperative neuroradiological follow-up was observed in patients with a tumour remnant and epilepsy. Given the fact that tumour relapse never occurred if GTR was performed, it is most likely sufficient to not obtain follow-up MRIs when a GTR has been proven (provided there is seizure freedom and histopathology is consistent WHO grade I). Although a recent study questions this point of view, demonstrating tumour recurrence in 8% after GTR (94), there is convincing evidence supporting the extremely low risk of tumour recurrence after GTR (85).

Long-term outcome and late effects in children with glioneuronal tumours (studies II and III)

Medical late effects

In the glioneuronal group neurologic long-term effects were seen sparsely. Only 13% had a minor neurological late effect that could be contributed to surgery when examined at follow-up, two with visual field defects and one with slight dysmetria/weakness in the left arm. However, scrutinizing the medical records demonstrated a lack of ophthalmological investigations as a part of routine follow-up after surgery; only 18% (3/17) of the patients with a temporal tumour had a postoperative check-up including assessment of visual acuity and visual fields. Endocrinological late effects were not seen.

Seizure outcome

In study II 64% (16/25) were seizure-free at follow-up (seizure freedom was defined as no seizure during the last two years with/without ongoing AED medication). Although GTR did not guarantee seizure freedom, it was a highly prognostic factor ($p=0.027$); seizure freedom was obtained in 82% if GTR was performed compared to 25% in the STR/biopsy group. Second-look surgery after a first postoperative MRI was never performed, but four patients were re-operated at a later stage due to a tumour remnant causing refractory epilepsy. A GTR resulting in seizure freedom was achieved in one of these four patients. Other factors like tumour location (temporal vs. extra-temporal), pre-operative seizure control (refractory vs. medically controlled), gender, age at symptom onset, preoperative epilepsy duration or tumour size did not significantly correlate with postoperative seizure outcome. Most of the seizure-free patients had been able to make a successful withdrawal of AED (75%). Although early post-operative seizure recurrence (within one year) was seen in most patients (67%) with epilepsy at follow-up, late seizure recurrence occurred in three patients despite GTR and no tumour recurrence on follow-up MRI (3, 11 and 14 years post-operatively). Approximately one third (9/25) had persistent epilepsy with ongoing seizures. Of these 55% (5/9) had refractory epilepsy, three of whom had a high seizure severity (i.e. the seizures prevented them from functioning at an acceptable level). Thus, long-term seizure outcome is good if GTR is achieved, but seizure outcome is not static. Most seizure recurrences correlates to incomplete resections and occur shortly after surgery, but late seizure recurrences can occur, even after GTR.

Cognitive outcome

In study III, 22 patients (22/24) agreed to participate in neuropsychological assessments with WISC-IV/WAIS-IV and RCFT. Regarding cognitive outcome at follow-up there were no significant differences between the seizure-free group ($n = 14$) and the epilepsy group ($n = 8$) with respect to the four

different index scores measuring specific cognitive domains (VCI, PRI, WMI, PSI) or FSIQ. Compared with a norm mean WISC-IV/WAIS-IV score of 100, both groups had lower scores for all indices, but significant reduction was only seen in the seizure-free group with respect to PRI, WMI, and FSIQ. A discrepancy of mean scores was found in the epilepsy group when comparing patients with low and high seizure severity, i.e., patients with high seizure severity had substantially lower scores on WISC-IV/WAIS-IV.

Cognitive outcome related to tumour location (defined as either left or right temporal or extratemporal) did not vary significantly, although patients with right temporal tumours had the highest scores in all indices except PSI. This difference in cognitive outcome regarding tumour location, i.e., patients with right temporal tumours performing better, might be attributed to a better chance of GTR, which in turn has an impact on seizure outcome. Only two patients with a right temporal tumour had remaining epilepsy, and both had a low seizure severity. However, larger study populations are needed to reveal possible significant differences in this respect. A correlation between resection of seizure foci and cognitive outcome in epilepsy surgery has been demonstrated in other studies (137).

Regarding age as a risk/prognostic factor, younger age at epilepsy onset seemed to correlate with lower scores on PSI ($r = 0.50$; $p = 0.018$) and FSIQ ($r = 0.38$; $p = 0.081$).

Regarding RCFT and immediate and delayed recall, there were no significant differences between the seizure-free group and the epilepsy group or against a norm T-score of 50. The same discrepancy regarding outcome was noted when comparing patients with low and high seizure severity, i.e., patients with high seizure severity did considerably worse.

Historical neuropsychological testing had been performed either preoperatively (named T1), two years postoperatively (named T2), or both. The results of these tests (WISC-III) were compared with data (WISC-IV or WAIS) gathered at the latest follow-up (named T3). Complete neuropsychological test data (T1–T3) were retrieved in 11 patients (of whom 9 were seizure-free). Significant gains in mean scores through T1 to T3 were observed in all five domains, except for PRI between T2 and T3. The same significant improvements over time (T1–T3) were seen for immediate and delayed recall regarding RCFT (Figure 4).

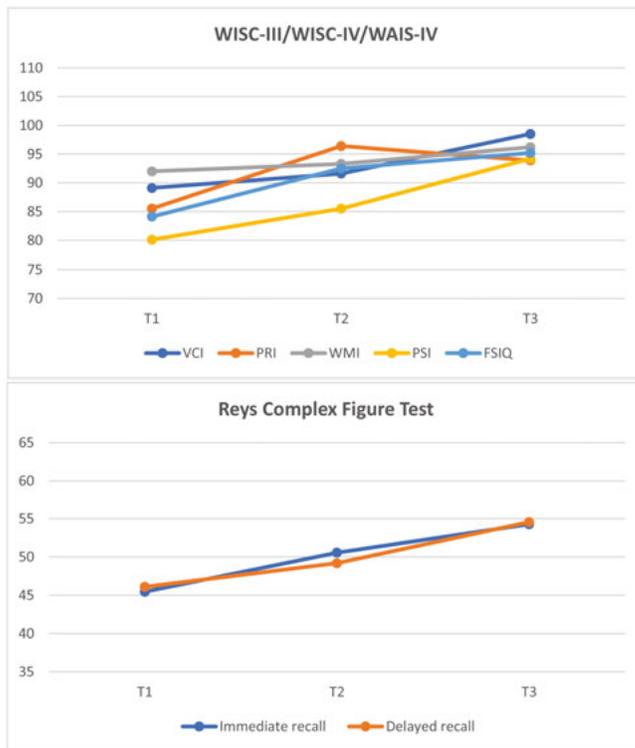


Figure 4 – Longitudinal data for both WISC-III/WISC-IV/WAIS-IV (index scores) and RCFT (T-scores) are presented (n=11). A successive gain in mean values for the specific cognitive domains (VCI, PRI, WMI, PSI), FSIQ, and immediate and delayed recall are noted, except for a reduction in PRI between T2 and T3. Significant changes were seen for all measures except WMI when comparing T1 with T3, analysed with the related samples Wilcoxon signed-rank test.

In summary, although there seems to be a risk for long-term cognitive problems, the above findings illustrate two important points: 1) Glioneuronal tumours cause significant pre-surgical cognitive impairment through high seizure frequency, and sometimes high seizure severity, together with undesirable side effects of AEDs, and 2) Seizure freedom or at least a low seizure severity allows cognitive restitution over time. Thus, on an individual basis we advocate for repeated clinical assessments beyond the two-year postoperative control, as this might be of great importance for schooling.

Psychosocial outcome (psychiatric, health-related quality of life, educational and vocational outcome)

Psychiatric outcome

Although most of the patients had normal values for HADS, 32 % of the adults exceeded the cut-off value for anxiety and 16% for depression despite seizure freedom. Comparable Swedish age-matched normative data for HADS are 28% (possible anxiety) and 7% (possible depression) (138). Eleven per cent had a lower self-esteem than normal. Two adolescents who completed BYI had low scores (<35th percentile) for anxiety and depression. These numbers, together with the finding that 38% of the patients were admitted some time postoperatively for a psychiatric evaluation at either child and adolescent or adult psychiatric services, suggest a risk for psychiatric symptoms despite a good chance of seizure freedom in the long run. Although skepticism has been raised using HADS as a screening tool for anxiety and depression (139-141), it is still widely used in this respect (142-145). Given our small population-based studies and the fact that depression and anxiety is a common comorbidity of epilepsy, more investigations on larger study populations would be of interest to further explore long-term psychiatric outcomes of children treated for glioneuronal tumours in childhood.

HRQoL outcome

Although most often not statistically significantly different, mean domain scores for SF-36v2 compared with a Swedish age-matched reference sample (n=2577) were almost consistently lower for both the seizure-free and epilepsy groups, the latter having considerably lower scores (Figure 5). The seizure free group had a significantly lower score than the reference on vitality (p=0.013) while the epilepsy group did significantly worse than the reference group on physical component summary (PCS; p=0.046). In between comparison of the seizure-free and epilepsy group demonstrated significantly better outcome for the seizure-free group on PCS (p=0.036). Although most of the SF-36v2 domains did not show significant differences in between groups, the trend of the curves in Figure 5 mimics that of the reference sample, supporting our interpretation that the data are robust.

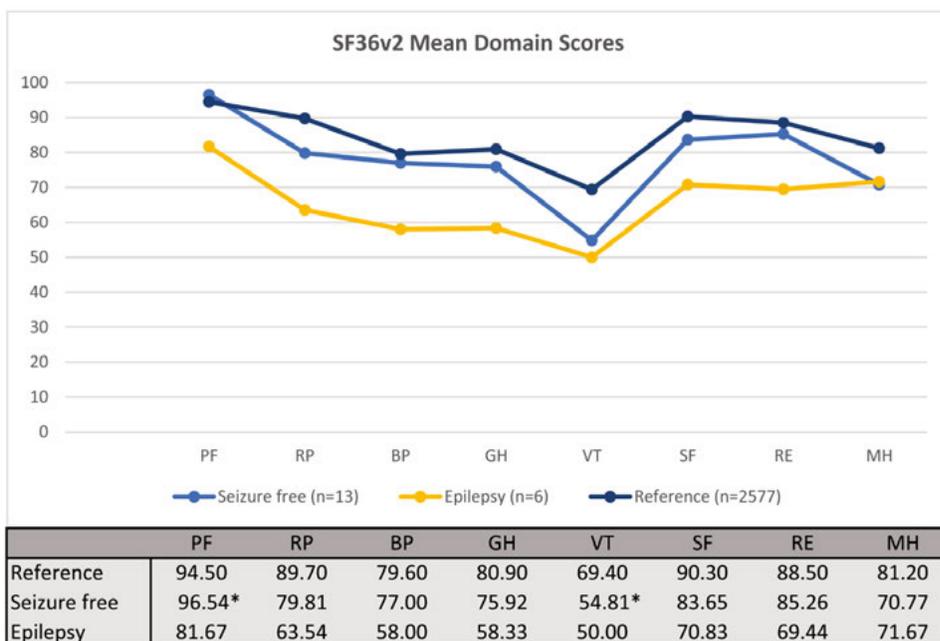


Figure 5 - Mean raw scores for the eight HRQoL domains in SF-36v2 in relation to seizure outcome: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Significant differences ($p < 0.05$) in relation to the reference sample are marked with an asterisk (*). Wilcoxon signed-rank test was used to compare outcomes of the seizure-free and the group with remaining epilepsy to an age-matched Swedish reference sample ($n=2577$). When comparing the seizure-free group and the epilepsy group, the independent samples Mann-Whitney U test was used.

Comparing QOLIE-31 scores between the seizure-free and epilepsy group demonstrated that the seizure-free group had significantly higher scores regarding seizure worry ($p=0.003$), medication effects ($p=0.024$) and social function ($p=0.01$). Also, when comparing with the norm values of QOLIE-31 (T-score of 50), the seizure-free group did significantly better on several domains (seizure worry ($p=0.001$), emotional well-being ($p=0.025$), medication effects ($p=0.001$), social function ($p=0.001$), and overall score ($p=0.003$)), while the epilepsy group did not. In the context of HRQoL, it is important to note that there was a discrepancy between patients with low and high seizure severity. Patients with a low seizure severity had a rather good quality of life. Thus, achieving seizure freedom or at least a low seizure severity seems to be important for long term HRQoL, a finding supported by other studies (142, 146, 147).

Educational and vocational outcome

Demographic characteristics relates to the adults included in the follow-up. Fifty per cent had continued their education after high school and 75% had employment (i.e. full time, part time or ongoing studies). When comparing the seizure-free and epilepsy group there seemed to be a discrepancy in educational and vocational outcome, i.e. seizure-free patients had a better outcome. All patients in the seizure-free group continued their education after elementary school compared to just 50% in the epilepsy group ($p=0.018$). Moreover, 64% in the seizure-free group were employed full time compared to 0% in the epilepsy group ($p=0.014$). People who were seizure-free also had a higher possibility of living in a relationship and having children, although not statistically significant.

Neuropathological findings (studies II and IV)

Association to FCD and “double” pathology

In study II we investigated the frequency of FCD in glioneuronal tumours of childhood. No convincing histopathological signs of FCD were demonstrated, except for one patient with architectural changes corresponding to FCD IIIb. Consequently, “double” pathology (i.e. FCD type IIa or IIb + glioneuronal tumour) was not found and thus, did not influence long-term seizure outcome. We consider this finding as robust since thorough microscopic evaluation and immunohistochemistry for both tumour specific markers (i.e. CD34, BRAFV600E in mutated tumour) and markers visualising architectonic cortical changes and presence of dysmorphic neurons (i.e. anti-Neu N, SMI31 and SMI32) were used to exclude remote LEAT tumour cell infiltration or the presence of small LEAT satellite clusters within brain tissue, which have been described in GGs and DNETs (58).

Frequency of glioneuronal tumour subgroups

In study IV, with the longest observational time of 22 years (1995–2016), a total of 33 patients with a neuropathological confirmed diagnosis of a glioneuronal tumour were re-classified according to the current WHO classification of the tumours of the central nervous system 2016 (12). In descending order, the most frequent subtypes were: GG (82%), DNET (12%), DIG and PGNT (both 3%). Other tumour subgroups were not seen, making them very rare. This is in line with most publications on LEATs specifying GGs as the commonest tumour type. However, poor inter-observer correlation is commonplace, particularly for GG and DNET, where an unexplained and geographical variability across surgical series suggests marked variability in diagnostic practice (58). Because of this, a new model for the classification of glioneuronal tumours, based on biological similarity rather than subjective histological examination, has been proposed to refine future cohorts (88).

None of the tumours in our cohort displayed any histological anaplastic or high-grade features, supporting earlier findings of the low-grade nature of glioneuronal tumours (58, 82, 85).

mTOR pathway activation and SSTR expression

Regarding SSTR expression, SSTR2a and SSTR3 were a frequent finding in GGs, with an IRS score ≥ 4 in 56% (15/27) and 44% (12/27) of the tumours, respectively. Expression of SSTR1 and SSTR5 was absent/low in all GGs. Moreover, signs of mTOR pathway activation were a prominent finding when analysing pS6, expressed with an IRS ≥ 4 in 100% of the GGs (27/27). IRS ≥ 4 for ERM were expressed in 22% (6/27). Details of SSTR expression and mTOR pathway activation in the GGs are depicted in Figure 6.

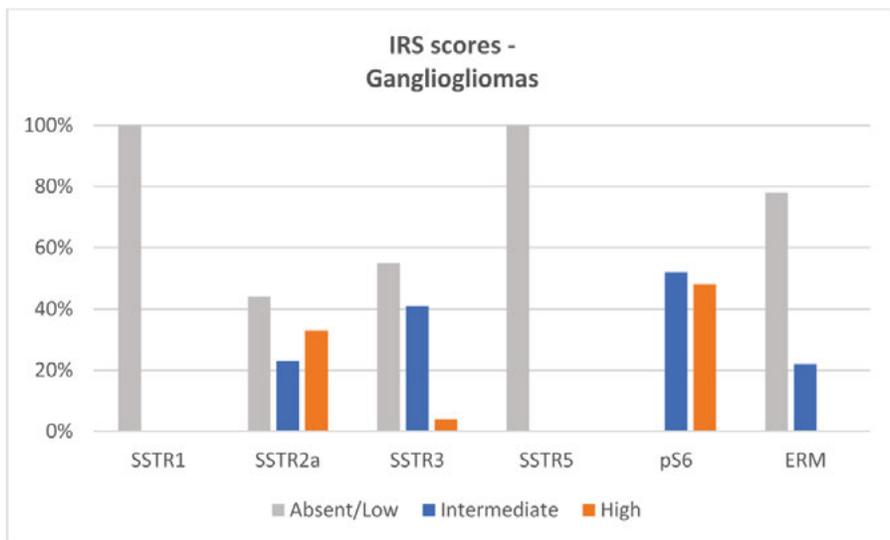


Figure 6 – Expression of SSTRs (SSTR1, 2a, 3 and 5) and mTOR pathway activation (pS6 and ERM) in all GGs (n=27) based on IRS scores corresponding to absent/low (0–3), intermediate (4–8) and high staining (9–12). An IRS score ≥ 4 was determined to be significant. SSTR2a, SSTR3 and pS6 are expressed to a high extent. (Expression of SSTR4 was not analysed, partly because SSTR4 is not significantly expressed in humans and partly because of the lack of any reliable monoclonal anti-SSTR4 antibody).

In the four DNETs, SSTR2a expression was the most frequent finding, with an IRS score ≥ 4 in 75% (3/4). Regarding the other SSTRs, significant expression of SSTR1 and SSTR3 was seen in 25% (1/4), whereas SSTR5 was negative, 0% in all the tumours (4/4). There were no signs of mTOR pathway activation in the DNETs, except for one tumour with an intermediate staining for pS6. There seemed to be a significantly higher frequency of mTOR pathway activation in GGs than in DNETs based on pS6 expression (p=0.001).

Due to the small number of DNETs, it is difficult to draw any further conclusions for this subgroup.

Demonstrating SSTRs, particularly SSTR2a and SSTR3, in glioneuronal tumours underpins a possible seizure-reducing effect and/or tumour-reducing effect of SAs in these patients. Moreover, the finding of mTOR pathway activation in paediatric GG might imply a possible dual therapeutic effect of mTOR inhibitors in patients with inoperable GGs, i.e. seizure- and tumour-volume-reducing effects. However, concerns have been raised observing “rapamycin resistance” – mTOR inhibitors may cause activation of a negative feedback loop inducing upstream receptor tyrosine kinase signalling, resulting in activation of the PI3K-Akt pathway and thereby attenuating their effect. Somatostatin analogues binding to SSTR2a might overcome this negative feedback loop by inhibiting tyrosine kinase signalling through activating phosphotyrosine phosphatase SHP-1, which dephosphorylates insulin receptor substrate-1 at the tyrosine residue. Thus, our finding of both SSTR2a expression and mTOR pathway activation in paediatric GGs may imply that combining the treatments can potentially carry positive additive effects on both seizures and tumour size.

BRAFV600E mutational status

Regarding BRAFV600E mutations, 48% (13/27) of the GGs were positive, while all DNETs were negative ($p=0.12$), supporting the use of BRAFV600E targeted therapy in inoperable BRAFV600E mutated GG demonstrating signs of progression. BRAFV600E mutational status was assessed by using immunohistochemistry with antibody targeting BRAFV600E mutated protein. Immunohistochemical analysis was combined with pyrosequencing based molecular genetic analysis in cases operated during recent years.

General remarks, strengths and limitations of the studies

In general, better long-term outcomes with respect to cognitive and psychosocial functioning, with better quality of life and a higher grade of employability are observed if seizure freedom can be achieved. This implies that long-term seizure freedom is of utmost importance and should be strived for. The material does not prove a correlation between the “wait and see” approach and any impairment of outcome measures, but a meta-analysis including 910 patients across 39 studies has observed significantly higher rates of seizure freedom if early operative intervention has been applied (79). By linking seizure freedom to better outcomes regarding psychosocial, cognitive function and quality of life, our studies support the need for early surgical intervention, which has

been proven to be safe. Timing of surgery should be a multi-professional decision; waiting until and beyond medical refractory epilepsy has been established seems to be a simplistic view.

The cohort in these population-based studies is a representative material of both the CNS tumour and glioneuronal tumour population in a tertiary referral centre for children with CNS tumours and medically refractory epilepsy in Sweden. All the registries that contain or might contain information on children and adolescents with CNS tumours or glioneuronal tumours have been included; hence we believe that we have been able to include all the patients diagnosed with a CNS tumour, including glioneuronal tumours in the health region. Moreover, the main aims of these studies were all related to a single subgroup of paediatric CNS tumours, i.e. glioneuronal tumours.

Regarding the follow-up studies II and III, a major advantage was the long postoperative follow-up time. All patients had a postoperative follow-up time exceeding five years, (mean: 12.1 years; range: 5.0–19.3), which is substantially longer than most previous follow-up studies concerning glioneuronal tumours. Furthermore, a very high proportion of the eligible patients accepted participation in study II and III, 89% and 86% respectively. Upon acceptance all interviews and investigations were done on site at Uppsala University Children's Hospital.

Re-evaluation of all accessible surgical tumour specimens was performed by experienced neuropathologists according to the latest WHO classification of tumours of the central nervous system available at the time for the different studies, either the 2007 (14) or the 2016 (12) classification .

The most obvious limitation is the small number of patients, which makes it difficult to obtain significant differences compared with norm values and across groups. Another disadvantage is the partially retrospective design and varying amounts of information from the medical records, although a thorough review of these was undertaken in all cases. Also, historical neuropsychological assessments and cognitive data were not complete. However, longitudinal data over three time points were available in a reasonable number of participants. Such data are extremely hard to obtain over a period of five to more than 10 years.

Clinical impressions

During my work and progress with this thesis I have had the good fortune of meeting patients (and some of their caregivers) and taking part of their medical histories. It seems improper for me not to have written down a couple of reflections upon these meetings. Some patients and caregivers have difficulties grasping a “wait and see” approach if a glioneuronal tumour, deemed amenable to neurosurgery (i.e. low risk of sequelae), causes epilepsy. One should be aware that this might cause even further psychological distress and affect quality of life, schooling, education and working capacity. This kind of psychological distress must be addressed and should be a “catalyst” for an epilepsy surgery evaluation. Moreover, most patients in this follow-up study were very favourable to the long-term follow-up. It gave them an opportunity to get answers and reflect upon years of medical controls during childhood, when their caregivers were responsible and made all decisions. Furthermore, they got an opportunity to discuss future risks. I firmly believe we should offer these patients an opportunity for a clinical follow-up in connection with transition to adulthood, a routine that is already being followed for other CNS tumour survivors in Sweden (i.e. SALUB controls at 18 years of age).

Conclusions

The most important conclusions from this thesis are:

- High frequencies of medical and neuropsychological late effects are found in children with both low- and high-grade CNS tumours.
- Glioneuronal tumours seem to be more common than previously reported, accounting for 13.5% of all the CNS tumours.
- Glioneuronal tumours often cause medically refractory epilepsy. Anti-epileptic drugs do not prevent the need of surgical intervention and, thus, are not a sustainable solution in the long run.
- Glioneuronal tumours cause significant pre-surgical cognitive impairment through high seizure frequency, and sometimes high seizure severity, combined with undesirable side effects of AEDs.
- Time from symptom debut until neurosurgery is often prolonged (i.e. many years) in children with glioneuronal tumours.
- In the setting of a dedicated epilepsy surgery team postoperative complications, and thus medical late effects, can be kept to a minimum.
- Long-term outcome is good regarding seizure freedom if GTR is achieved, but late seizure recurrence can occur.
- Postoperative seizure freedom or at least low seizure severity provides a good possibility of cognitive restitution although the results are not comparable with the norm (i.e. long-term cognitive difficulties exist). However, cognitive restitution takes time and is not necessarily seen at the two-year postoperative follow-up.
- Achieving seizure freedom is important for educational and vocational outcome.
- Although lower than in corresponding reference groups, HRQoL is good if seizure freedom or at least a low seizure severity can be achieved.
- Children treated for glioneuronal tumours seem to have an increased risk for depression.
- SSTR2a and 3 are expressed in a significant proportion of paediatric glioneuronal tumours. Expression of pS6 in all GGs indicates activation of the mTOR pathway. Somatostatin analogues and

mTOR inhibitors or a combination of these, might represent potential therapeutic alternatives for a subgroup of patients with inoperable tumours or tumour remnants causing a medically refractory epilepsy or tumour growth.

Clinical implications and future perspectives

Based on the findings and earlier studies we advocate for:

- The “wait and see” approach should be abandoned – early surgical intervention is recommended and should be considered and prioritized as a first-line treatment.
- Long-term clinical follow-up should be offered to all patients with a glioneuronal tumour. A rehabilitation team, including a paediatric/adult neurologist, a neuropsychologist and a special education teacher, is a way to accommodate this need and should be offered at least to all patients with remaining epilepsy despite earlier lesionectomy.

Regarding future research it would be of interest to perform a prospective nationwide (or Nordic) study of glioneuronal tumours and FCDs to collect broad data about possible prognostic factors and longitudinal data related to different outcome measures. This could give us better insight into both short and long-term outcomes important for our design of postoperative care and surveillance. Furthermore, shortening the preoperative epilepsy duration for patients with glioneuronal tumours is an important factor to improve long-term outcomes. To achieve this goal, we must pinpoint the causes of delay in the care chain: the patient’s delay, the doctor’s delay in diagnosing a glioneuronal tumour, late referrals to but also delays within a tertiary referral centre for children with CNS tumours and medically refractory epilepsies are all of concern. Future work and research should focus on both raising the awareness of and facilitating epilepsy surgery as a possible first-line treatment. In today’s medical era with constant ongoing discussions about centralisation of highly specialised hospital care, it is important to keep this in mind – will fewer centres cope with a growing demand and be able to deliver efficient high-quality care?

Apart from larger study populations, qualitative studies might also give important insights, which can improve patient care and outcome. Moreover, it is important to find new therapies and interventions coping with cognitive dysfunction.

Another future challenge is to develop new AEDs that not only provide symptomatic relief through preventing seizures but also interact with processes of

importance for epileptogenesis. Neuropeptides could be a way forward, and our finding of SSTR2a and to a lesser extent SSTR3, but also mTOR pathway activation in GGs can support a pilot study of SAs and/or mTOR inhibitors in a subgroup of patients with inoperable tumours or tumour remnants causing medically refractory epilepsy or tumour growth.

Sammanfattning på svenska

Bakgrund

Hjärn- och ryggmärgstumörer (CNS-tumörer) är näst efter leukemier den vanligaste maligna sjukdomen hos barn och ungdomar. Trots förbättrade behandlingsalternativ med kirurgi, strålning samt cellgifter kan man i långtidsuppföljningar observera seneflekter i form av bland annat kognitiv påverkan, hormonell dysfunktion, fin- och grovmotoriska svårigheter samt psykosociala problem. Brister i kognitiv utveckling har framförallt beskrivits hos barn och ungdomar med högmaligna hjärntumörer (WHO grad III – IV). Lågmaligna hjärntumörer (WHO grad I – II) är däremot inte lika väl beskrivna.

Glioneuronala tumörer är en undergrupp av lågmaligna hjärntumörer, vilka nästan alltid ger upphov till epilepsi, som kan vara mycket svårbehandlad med dagens mediciner (terapieresistent). Möjlighet till anfallsfrihet är dock god om tumören kan opereras radikalt, dvs. tas bort i sin helhet. Barn och ungdomar med glioneuronala tumörer förväntas ha mycket god långtidsöverlevnad, men det saknas uppföljningar som visar hur det går på lång sikt.

Eftersom en del barn och ungdomar har en inoperabel glioneuronal tumör, som leder till en terapieresistent epilepsi, finns det ett behov av att hitta alternativa behandlingsvägar. Syntetiska somatostatinanaloger, med verkningsmekanism via somatostatinreceptorer (SSTR), har visat sig kunna ha tumörreducerande effekt vid flera, huvudsakligen neuroendokrina tumörtyper. Utöver detta har även somatostatin visat sig ha anfallsreducerande effekt i djurmodeller. ”Mammalian target of rapamycin” (mTOR) är överaktiverat vid den neurologiska sjukdomen tuberös skleros, som kan orsaka både svår epilepsi och hjärntumörer. Hos patienter med tuberös skleros har mTOR-hämmare visat sig ha både tumör- och anfallsreducerande effekt.

Målsättning och frågeställningar

Det övergripande ändamålet har varit att långsiktigt studera följd effekterna av hjärntumörer och dess behandling på barn- och ungdomar i Uppsala-Örebroregionen. Särskild tonvikt har lagts på glioneuronala tumörer. Huvudsakliga frågeställningar, som har studerats i fyra olika delarbeten, har varit följande:

Studie I –

Att beskriva kliniska karakteristika och undersöka förekomsten av neurologiska, endokrinologiska och kognitiva seneffekter hos barn och ungdomar med hjärntumörer.

Studie II –

Att ge en detaljerad klinisk beskrivning av en grupp barn och ungdomar med glioneuronal tumör och att studera långtidsprognos med avseende på epilepsi, neurologiska seneffekter och möjligheter till sysselsättning i form av studier och arbete.

Studie III –

Att studera långtidsprognos hos barn och ungdomar med glioneuronal tumör med avseende på kognitiva svårigheter, hälsorelaterad livskvalitet och psykiatrisk problematik.

Studie IV –

Att studera om SSTR och mTOR aktivering förekommer i glioneuronala tumörer hos barn och ungdomar.

Viktigaste fynd i avhandlingen

Medicinska seneffekter med neurologiska och kognitiva svårigheter är vanligt förekommande även hos barn och ungdomar med låggradiga hjärntumörer. Glioneuronala tumörer utgjorde 13,5% av det totala antalet hjärntumörer och verkar därmed vara vanligare än vad som tidigare beskrivits. De ger nästan alltid upphov till epilepsi, som i många fall blir terapieresistent och orsakar en kognitiv påverkan. En absolut majoritet av barn och ungdomar med glioneuronal tumör blir förr eller senare föremål för operation, som kan utföras säkert med mycket liten risk för neurologiska komplikationer. Radikal operation (dvs. borttagande av hela tumören) av glioneuronala tumörer kan uppnås i hög utsträckning, och är en av de viktigaste prognostiska faktorerna för långsiktig anfallsfrihet, även om det finns en viss risk för sena anfallsrecidiv. Tiden från symptomdebut till neurokirurgisk åtgärd är dock i många fall väldigt lång (flera år), vilket påverkar långtidsprognosen för dessa patienter. Diagnostik och ställningstagande till operation behöver drivas mer skyndsamt än vad som är fallet i nuläget.

Det verkar finnas en överrepresentation av psykisk ohälsa hos barn och ungdomar med glioneuronal tumör, både på kort och lång sikt. Att uppnå långsiktig anfallsfrihet är av stor betydelse, eftersom det är tydligt kopplat till bättre prognos vad gäller kognitiva svårigheter, hälsorelaterad livskvalitet och möj-

ligheter till fortsatta studier och framtida arbete. En kognitiv återhämtning efter svårbehandlad epilepsi och epilepsikirurgi verkar dock vara en långsam process. Dagens nationella riktlinjer som förespråkar klinisk uppföljning två år postoperativt är sannolikt inte tillräckliga utan behöver individualiseras och förlängas.

En del patienter kan inte erbjudas radikal operation, vilket ökar risken för kvarstående terapist resistant epilepsi och även tumörprogress. Eftersom glioneuronala tumörer, i synnerhet undergruppen gangliogliom, uttrycker SSTR2a och SSTR3 samt att mTOR aktivering finns kan somatostatinanaloger och/eller mTOR hämmare vara en möjlig framtida behandlingsväg.

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