

Research Project Report

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**Health-related quality of life (HRQL) of children and adolescents following
encephalitis and its relationship with everyday memory and executive
function: Parent/carer report**

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Abstract

Objective- Following encephalitis, children can experience neuropsychological, psychological and medical consequences, making health-related quality of life (HRQL) of particular interest in this clinical population. To explore this under-researched topic area, this study was designed to investigate whether a relationship exists between the two most frequently reported neuropsychological consequences of childhood encephalitis (parent/carer reported executive function and everyday memory problems) and parent/carer reported HRQL. In addition, it explored to what extent these and other illness specific factors are predictors of parent/carer reported HRQL in children following encephalitis.

Design- The study took an exploratory cross-sectional design. Parametric and non-parametric correlations were employed to test the primary hypotheses and consider whether further illness-specific factors were related to parent/carer reported HRQL. Those variables found to correlate significantly with parent/carer reported HRQL were entered into a multiple linear regression to consider how predictive they were of HRQL.

Method- Thirty-eight parents/carers of children/adolescents, aged eight – 15 years old, who had a history of encephalitis responded to an invitation to take part. Participants were recruited through the Encephalitis Society's database of families with children/adolescents who had been diagnosed with encephalitis at

any time during childhood. Each parent/carer completed a Pediatric Quality of Life Inventory™ (PedsQL™), a Behaviour Rating Inventory of Executive Function (BRIEF), a Children's Memory Questionnaire (CMQ), and a demographic/illness specific questionnaire in relation to their child. Parents/carers of potential participants were sent a recruitment pack by post and asked to return the measures in a stamped addressed envelope should they wish to take part. Where possible, children/adolescents were asked to provide their assent to take part and their parent/carer was asked to provide their consent to provide information in relation to their child.

Results- Parent/carer reported everyday memory problems and executive function impairment were found to significantly negatively correlate with parent/carer reported HRQL. Further exploratory analysis found that sleep difficulties significantly correlated with parent/carer reported HRQL, while age at time of illness and diagnosis of epilepsy did not correlate significantly with parent/carer reported HRQL. Through a forced entry multiple linear regression analysis, combined parent/carer reported everyday memory, executive function and sleep difficulties were found to account for up to 71% of the variance of parental-reported HRQL, with everyday memory being the most statistically significant predictor.

Conclusions- Frequently reported neuropsychological impairments following childhood encephalitis are found to relate significantly to parent/carer reported

HRQL. This indicates important implications for children, and their families, following encephalitis, and suggests areas for specific intervention and rehabilitation. The finding of a significant relationship between parent/carer reported sleep difficulties and parent/carer reported HRQL is consistent with findings in general, and other health condition, populations. The finding of no significant relationship between the variables of age at time of illness, diagnosis of epilepsy and parent/carer reported HRQL is inconsistent with studies in other clinical populations, and warrants further investigation. Consideration of the findings, and their implications for clinical practice, are discussed. Consideration is given to the small sample size and recommendations for further research are proposed.

Statement of contribution

This study was designed and ethical approval sought by the author of this paper. Identification of potential participants was carried out by the Encephalitis Society. All recruitment packs were prepared by the author before being sent out by the Encephalitis Society to all participants on their database who met the inclusion criteria for the study. All questionnaires and assessments were scored, entered into a statistical analysis programme and analysed by the author. Academic research supervision was obtained by the author from Dr Shirley Thomas and Dr Aidan Hart, Academic Tutors, and clinical research supervision from Dr Arleta Starza-Smith, Consultant Paediatric Neuropsychologist.

The author is grateful to the Encephalitis Society for their help in locating the participants and to the families who took part.

Journal Paper

This journal paper is in the format of that to be submitted to the British Journal of Clinical Psychology

Abstract

Objectives- Following encephalitis, children can experience neuropsychological, psychological and medical consequences, making health-related quality of life (HRQL) of particular interest in this clinical population. This study was designed to investigate whether relationships exist between the two most frequently reported neuropsychological consequences of encephalitis (parent/carer reported executive function and everyday memory problems) and parent/carer reported HRQL. In addition, it explored to what extent these and other illness specific factors are predictors of parent/carer reported HRQL.

Design- This study took an exploratory cross-sectional design. Correlations and multiple linear regression were applied to explore primary and exploratory hypotheses.

Method- Thirty-eight parents/carers of children/adolescents, aged 8 – 15 years old, who had a history of encephalitis responded to an invitation to take part. Participants were recruited through the Encephalitis Society. Each parent/carer

completed a Pediatric Quality of Life Inventory™ (PedsQL™), a Behaviour Rating Inventory of Executive Function (BRIEF), a Children's Memory Questionnaire (CMQ), and a demographic/illness specific questionnaire in relation to their child.

Results- Parent/carer reported everyday memory, executive function and sleep difficulties were found to significantly correlate with parent/carer reported HRQL. Combined, these sequelae were found to account for up to 71% of the variance of parental-reported HRQL, with everyday memory being the most statistically significant predictor.

Conclusion- Frequently reported neuropsychological impairments, and sleep difficulties, following childhood encephalitis are found to relate significantly to parent/carer reported HRQL. This indicates important implications for children post-encephalitis and suggests specific areas for rehabilitation. Consideration is given to the small sample size and recommendations for further research are proposed.

Introduction

Advances in medicine have significantly improved the outcome of encephalitis in childhood (McGrath, Anderson, Croxson & Powell, 1997; Skoldenberg et al., 1984; Whitley et al., 1986). Despite this, childhood encephalitis continues to be associated with mortality (Granerod & Crowcroft, 2007), and figures suggest that up to two thirds of survivors experience severe neurological consequences such as epilepsy, hemiplegia and cognitive impairment (Elbers et al., 2007). This raises concerns regarding the health-related quality of life (HRQL) of children following such a potentially fatal illness. This paper will present a review of the literature concerning encephalitis in childhood, identify concerns regarding children's HRQL post-encephalitis and detail the current study's investigation into this topic area.

Encephalitis is an inflammation of brain tissue that can result from a number of viral, bacterial or parasitic agents (e.g. herpes simplex virus (HSV), varicella zoster virus (VZV), tick born encephalitis), or from an atypical immune response, such as that triggered by a recent viral infection or vaccination (e.g. acute disseminated encephalomyelitis (ADEM)) (Stone & Hawkins, 2007) (see extended background 1.1. for further information on causative agents).

Prevalence of encephalitis is found to be higher in the paediatric population, with incidence figures for the UK quoted as 1.5 per 100,000 in the general

population, 2.8 per 100,000 in children and 8.7 per 100,000 in infants under the age of one (Health Protection Agency, 2005). Despite higher incidence in children there continues to be a dearth of literature specific to outcome following childhood encephalitis (see extended background 1.2 for worldwide incidence of encephalitis).

Whilst encephalitis can present as a chronic condition, it is most commonly observed as acute, with symptoms such as fever, headache, altered consciousness, focal neurology and seizures (Roos, 1999; Stone & Hawkins, 2007). Presentation, diagnosis, treatment and outcome can vary greatly due to the large number of causative agents that have been recognised (Granerod & Crowcroft, 2007; Tunkel, et al., 2008). Despite this, in many cases the aetiology remains unknown (Davison, Crowcroft, Ramsay, Brown, & Andrews, 2003; Tunkel et al., 2008) (see extended background 1.1 for further information on causative agents).

Encephalitis is an illness that can progress quickly and be difficult to diagnose due to the non-specific nature of symptoms at the onset of illness (Campbell, Linc & Muttersbaugh, 1998; Glaser et al., 2003). Following identification and diagnosis, however, timely treatment is imperative and has been found to significantly affect outcome (Elbers et al., 2007; McGrath et al., 1997). McGrath et al. (1997) report a reduction in mortality from 70% to 30% when treated with the anti-viral treatment acyclovir. In addition, survival rates are found to be

improved if treatment is initiated within four days of the onset of illness (Marton, Gotlieb-Steimatsky, Klein & Arlazoroff, 1996; Whitley & Gnann, 2002). Timeliness of diagnosis and treatment, and the length of time of treatment also impact on outcome. Elbers et al. (2007) identified a reduction from 71% of children developing adverse neurological outcomes following acyclovir treatment for 14 days, as opposed to 55% following treatment for 21 days (see extended background 1.3 for further information on treatment and outcome with acyclovir).

Specific damage can be caused to the temporal and orbito-frontal regions of the brain post-encephalitis (Campbell et al., 1998; Hokkanen & Launes, 2007; Kapur et al., 1994), and neuroimaging studies have observed specific patterns of brain damage in patients with encephalitis caused by particular causative agents (Tunkel et al., 2008). For example, patients with HSV encephalitis can display significant oedema and haemorrhaging in the temporal lobes (Tunkel et al., 2008).

Studies investigating long-term consequences of encephalitis in childhood have indicated significant neurological and neuropsychological sequelae, such as cognitive impairment, behavioural and personality problems and epilepsy (Benjamin et al., 2007; Dowell, Easton, & Solomon, 2001; Hooper, Williams, Wall, & Chua, 2007; McGrath et al., 1997; Smyth, Ozanne, & Woodhouse, 1990; Van-Schoor, Naude, van-Rensburg, Pretorius, & Boon, 2005; Whitley,

2006) (see extended background 1.4 for discussion of differences between childhood and adulthood encephalitis).

Consistent with the findings of specific damage to the temporal and orbito-frontal regions of the brain, frequently reported difficulties post-encephalitis include memory and executive function impairments (Dowell et al., 2001; Kneen & Solomon, 2007). A number of studies have identified memory problems as commonly reported sequelae of encephalitis in children (Benedict, Shapiro, Duffner & Jaeger, 1998; Benjamin et al., 2007; Dowell et al., 2001; McGrath et al., 1997; Wood, Brown & Felton, 1989). With memory having a significant implication for learning, this is a particular risk for children, where memory problems may have an important bearing on educational progress (Hooper et al., 2007; Kneen & Solomon, 2007). Executive function impairments, including difficulties with impulsivity, planning, and sustaining and shifting attention, are commonly reported following encephalitis in childhood (Dowell et al., 2001; Kneen & Solomon, 2007). These difficulties are reflected in a study by Dowell et al. (2001) in which 60% of children post-encephalitis were reported to experience difficulties with new learning and 72% with difficulties in attention and concentration.

Children are reported to be twice as likely as adults to experience epilepsy post-encephalitis (Dowell et al., 2001), and 67% have been found to show evidence of neurological impairment at time of hospital discharge (Klein, Hom,

Anderson, Latrizza & Toltzis, 1994). The impact of encephalitis on a child's psycho-social functioning has also been observed. Dowell et al. (2001) have highlighted difficulties reported by those who contracted encephalitis as children as including tiredness/fatigue (68%), mood swings (66%), anxiety (55%), frustration/anger (65%) and concentration/attention (72%). Sleep difficulties for children post-encephalitis are also reported (Encephalitis Society, 2005). Research has also highlighted the consequences of children's executive function difficulties post-encephalitis on parental distress, coping and parenting styles (Hooper et al., 2007).

(See extended background 1.5 for further discussion of the sequelae of encephalitis).

Whilst the literature demonstrates specific patterns of impairment, it also indicates that the consequences of encephalitis can be heterogeneous and wide ranging, with individual differences in observed outcome. Factors that have been shown to contribute to these differences include age at onset of encephalitis (Dowell et al., 2001; Rautonen, Koskiniemi & Vaheri, 1991), timing (Jablkowski, Kolasa, Szubert & Bialkowska, 2004) and length of treatment (Elbers et al., 2007), and level of consciousness at the time of presentation (Lahat et al., 1999). It has been shown that contracting encephalitis at a very young age, when the brain has not fully developed and cognitive functions have not yet been fully established can be devastating with the potential for long-term

neurological and neuropsychological outcome (Starza-Smith, Talbot & Grant, 2007).

Health-related quality of life (HRQL) has been described as specifically referring to the impact of health and illness on an individual's well-being in psychological, social, occupational and educational domains (Eiser & Morse, 2001). With the potential for children post-encephalitis to experience difficulties in many physical, psycho-social and educational domains, it must be questioned whether these factors impact on their HRQL. However, no research could be found that has specifically investigated HRQL in this clinical population.

Previous research has explored HRQL in children with other neurological conditions such as epilepsy (Ronen, Streiner & Rosenbaum, 2003; Sherman, Slick & Eyrl, 2006), attention-deficit hyperactivity disorder (ADHD) (Klassen, Miller & Fine, 2004) and traumatic brain injury (TBI) (Souza, Braga, Filho & Dellatolas, 2007; Stancin et al., 2002). These studies have indicated increased risks to HRQL for those children experiencing these neurological conditions and outcomes.

Important justifications for exploring HRQL in children with specific health conditions include reviewing the impact of a condition and its treatment on children, developing knowledge to prepare families and professionals for the likely difficulties following illness or treatment, and the potential for improving

HRQL through highlighting areas of particular concern (McGee, 1994). Factors that have been highlighted as important considerations when looking at child HRQL are the use of self- or parent-proxy measure, the use of disease-specific versus generic measures and the importance of evaluating the reliability and validity of measures (Eiser & Morse, 2001).

(See extended background 1.6 for further discussion on assessing HRQL in children).

Reviewing the literature has demonstrated that commonly reported sequelae for children post-encephalitis include epilepsy, executive function and memory difficulties (Dowell et al., 2001; Benjamin et al., 2007; Hooper et al., 2007; McGrath et al., 1997; Smyth et al., 1990; Van-Schoor et al., 2005; Whitley, 2006). However, it also highlights that children can present heterogeneously, with clinical outcome ranging from good recovery to severe impairment or fatality (Starza-Smith et al., 2007). With children post-encephalitis demonstrating some similarities but also at times wide variation in outcome, it does not appear justified to compare them directly to children with a primary diagnosis of epilepsy, ADHD, or children with TBI, and this has been highlighted by researchers and those working in clinical neuropsychology settings (Hooper et al., 2007; Starza-Smith et al., 2007).

In order to open up exploration into the topic of children/adolescents' HRQL post-encephalitis, this study took two stages. The primary aims of this study were to explore whether a relationship exists between frequently reported neuropsychological consequences and HRQL post-encephalitis in children, by testing out the following two experimental hypotheses;

Hypothesis 1 - A statistically significant relationship will be observed between parent/carer reported executive function impairment and parent/carer reported HRQL in children and adolescents post-encephalitis.

Hypothesis 2 - A statistically significant relationship will be observed between parent/carer reported everyday memory problems and parent/carer reported HRQL in children and adolescents post-encephalitis.

Due to additional illness specific factors, such as age at time of illness, length of time of acyclovir treatment, diagnosis of epilepsy and presence of sleep difficulties known to impact on outcome following acquired brain injury, it was important to further explore if there were additional relationships between these variables and parent/carer reported HRQL. For example, HRQL has been observed to be lower in children with epilepsy (Ronen et al., 2003) and with children experiencing sleep problems (Mitchell & Kelly, 2008). It was imperative that these variables were considered as many children post-encephalitis are diagnosed with epilepsy (Dowell et al., 2001) and many experience sleep

difficulties post-illness (Encephalitis Society, 2005). Therefore, the study secondly explored to what extent parent/carer reported memory and executive function impairments and other demographic/illness specific factors, such as age at onset, length of acyclovir treatment, diagnosis of epilepsy, and presence of sleep difficulties are predictors of HRQL following childhood encephalitis.

This study looked to highlight key areas of investigation for treatment and rehabilitation in medical, neuropsychological and psychological domains. It hoped to move forward from simply highlighting the neuropsychological and neurological consequences of encephalitis in childhood and to explore whether, and to what extent, these and other illness specific factors have an impact on children/adolescents' parent/carer reported HRQL. It was intended that this would help to inform clinical practice and provide information to help prepare families regarding expectations post-encephalitis. It hoped to highlight areas of need for rehabilitation, particularly in light of specific rehabilitation services for children with acquired brain injury (ABI) in the UK being limited (Crouchman, 1998; Hawley, Ward, Magney & Long, 2002). As well as identify key areas for further research.

Method

Participants

Participants were the parents/carers of children/adolescents aged eight – 15 years old who had a history of encephalitis (see extended background 1.7 for discussion of inclusion and exclusion criteria). Participants were recruited through the Encephalitis Society's database, with 171 families being invited to take part. Each child/adolescent was asked to give their assent and a parent/carer to give their consent in order to provide data with respect to the child (see extended background 1.8 for further discussion on use of parent/carer report). Thirty-eight participants responded to the invitation to take part. Due to five participants returning incomplete measures, only 33 children/adolescents were included in the final sample size (see extended background 1.9 for further discussion on sample size and extended results 2.1 for further discussion of missing data).

Demographic information for all 33 children/adolescents is detailed in Table 1. Consistent with prevalence rates detailed in the literature (Health Protection Agency, 2005), there is a negative skew for age at onset of illness with the mean age being 3 years old and 49% of children/adolescents experiencing encephalitis before their third birthday. Age of participants at the time of the study demonstrated full range from eight – 15 years old.

Table 1. Child Demographic Information (N = 33)

	<i>n</i>	<i>%</i>
<i>Gender</i>		
Male	15	45.5
Female	18	54.5
<i>Ethnicity</i>		
White British	29	87.9
White Irish	1	3
White & Asian	1	3
White other	2	6.1
	<i>M</i>	<i>SD</i>
<i>Age</i>	11.52	2.37
<i>Age at time of illness</i>	3.42	2.94

Measures

The Pediatric Quality of Life Inventory™ (PedsQL™) 4.0 Generic Core Scale (Varni, Seid & Rode 1999)

The parent-proxy version of the PedsQL™ was used as a measure of the child's parent/carer reported HRQL. This 23-item core measure of HRQL includes items that assess physical, emotional, social and school functioning. A

five-point Likert scale is utilised across all 23 items (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse scored and linearly transformed to a 0 – 100 scale, with higher scores indicating a better HRQL. A physical health and psychosocial health summary score can also be computed. Versions are available for different age ranges (8 – 12 years and 13 – 18 years) in order to account for developmental changes.

The parent-proxy version of the PedsQL™ has shown to be a feasible, reliable and valid measure of HRQL in children aged two – 16 years with and without chronic conditions (Varni, Limbers & Burwinkle, 2007). Its higher levels of objectiveness in comparison to other HRQL measures have deemed it more applicable as a proxy-measure (Upton, Lawford & Eiser, 2008). This measure was chosen due to its reliability and validity, applicability to a range of acute and chronic health conditions, quick and straightforward application, and measurement of a range of quality of life factors (see extended background 1.10 for further discussion of PedsQL™).

Drysdale, Shores & Levick (2004) Children's Memory Questionnaire (CMQ)

The CMQ was completed by the parent/carer with regards to their child in order to gain a measure of the child's everyday memory. The CMQ was compiled from two versions of the Everyday Memory Questionnaire (EMQ) developed for

adults (Sunderland, Harris & Baddeley, 1983; Sunderland, Harris & Gleave, 1984). The 34-item questionnaire asks parents/carers to consider a list of problems children might experience with memory and rate how often their child experiences each problem by circling a number between 1 and 7 (1 = never or almost never happens; 2 = about once in 3 months; 3 = about once a month; 4 = about once in 1–2 weeks; 5 = about once or twice a week; 6 = about once a day; 7 = more than once a day). Ratings for each questionnaire item are totalled, with a higher score indicating greater everyday memory problems. When utilised on a sample of healthy school children, the mean score was 72.89 (SD = 34.41), with a minimum score of 34 and a maximum score of 238.

The CMQ has been found to have high internal consistency (0.96), test-retest reliability (0.92) and high negative predictive power (Drysdale et al., 2004). This measure was chosen as it had been shown to be applicable to children/adolescents, provided a measure of children's everyday memory difficulties through parental/carer report, and was quick and straightforward to complete (see extended background 1.11 for further discussion of CMQ).

The Behaviour Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy & Kenworthy, 2000)

The parent form of the BRIEF was completed by the parent/carer to provide a measure of the child's executive function. The BRIEF is an 86-item assessment

of executive function for children aged five – 18 years. The BRIEF comprises two indices, the Behavioural Regulation Index (BRI), consisting of three clinical scales; inhibit, shift and emotional control, and the Metacognition Index (MI), consisting of five clinical scales; initiate, working memory, plan/organise, organisation of materials, and monitor. An overall Global Executive Composite (GEC) score is then computed. The raw scores are computed to T-scores (Mean = 50 and Standard Deviation = 10). T scores >65 indicate clinically significant impairment (Gioia et al., 2000). This study focused on the BRI, MI and GEC scores.

The BRIEF has been found to have high internal consistency (alpha coefficients =0.80-0.98) and test-retest reliability (0.82 for parents questionnaire). In addition, its convergent validity has been recognised against other measures of inattention, impulsivity and learning skills, and divergent validity has been demonstrated against measures of emotional and behavioural functioning (Gioia et al., 2000). The BRIEF was chosen for this study due to its utility in measuring executive function difficulties, its reliability and validity, and its ease of administration to complete (see extended background 1.12 for further discussion of the BRIEF).

A further short demographic/illness-specific questionnaire devised by the investigator requested the following information:

- Gender
- Age of child
- Age at time of illness
- Type of encephalitis
- If and for how long their child received acyclovir
- If the child had a diagnosis of epilepsy since encephalitis
- Pre-morbid chronic health or developmental conditions
- Any chronic health conditions since encephalitis
- Whether the child experienced sleep difficulties since encephalitis

Demographic/illness-specific information was collected in order to provide detailed information regarding participants. As well as defining the clinical sample, this information was collected in order to consider illness-specific factors and their relationship with HRQL, as planned for the secondary exploratory stage of the study (see extended background 1.13 for further discussion on demographic/illness specific questionnaire).

Procedure

Parents/carers of any children/adolescents on the Encephalitis Society's database, who met the inclusion criteria, were sent a recruitment pack through the post. This included the following:

- Invitation letter (see extended paper appendix A)
- Parent/carer information sheet (see extended paper appendix B)
- Child (8–10 years old) information sheet (see extended paper appendix C)
- Child/adolescent (11–15 years old) information sheet (see extended paper appendix D)
- Parents/carer consent form (see extended paper appendix E)
- Child/adolescent assent form (see extended paper appendix F)
- Age appropriate PedsQL™
- BRIEF
- CMQ
- Demographic/Illness-specific questionnaire (see extended paper appendix G)
- Stamped addressed envelope

Potential children/adolescents ages were identified through the database and the age appropriate measures sent. Parents/carers were invited to read the information sheet and, if agreeable, to complete the parental/carer consent form. The inclusion criteria included parents/carers and children/adolescents being able to read and understand English due to measures being written and standardised for English speaking populations. The parent/carer was asked to read the child/adolescent information sheet with their child and where possible ask them to provide their assent. Parent/carers were asked to complete the

measures and post them back to the investigator with the consent form and child's assent form (where possible) (see extended background 1.14 for further information on the Encephalitis Society and recruitment procedure).

Ethical approval was received from the Leicestershire, Northamptonshire and Rutland NHS Research Ethics Committee 2, the University of Lincoln Psychology Ethics Committee and agreement from the Encephalitis Society (see extended background 1.15 for further discussion of ethical considerations and journal paper appendix B and C for NHS and University ethical approval letters).

Statistical analyses

Data was analysed using SPSS version 17.0 (SPSS Inc., 2009). The distribution of scores was normal for the PedsQL™ total health score and CMQ. The variables of age, age at onset and GEC were found to be not normally distributed. Therefore, a parametric Pearson's r correlation was utilised to investigate hypothesis 2 and a non-parametric Spearman's ρ correlation for hypothesis 1. (See extended results 2.2 for further analysis of distribution of data).

Further non-parametric correlations were conducted between demographic/illness specific variables and HRQL. This included age at time of

illness, diagnosis of epilepsy and sleep difficulties. Point bi-serial correlations were used for diagnosis of epilepsy and sleep difficulties due to these being dichotomous variables with a yes or no response. It was not possible for other variables such as type of encephalitis, or length of time of treatment to be explored further, due to missing data or parent/carers being unsure of details of their child's illness (see 2.1 for discussion on missing data). All correlations were exploratory and were therefore two-tailed. A Bonferroni correction was applied to account for multiple comparisons, with an alpha level of 0.002 being used for all correlational analyses (see extended results 2.3 for discussion of Bonferroni correction).

A forced entry multiple linear regression was carried out with variables that correlated significantly with the PedsQL™ total health score. As the outcome variable of parent/carer reported total HRQL was normally distributed, the data was considered to meet the assumptions for conducting a multiple regression (Dancey and Reidy, 2007) (see extended results 2.7 for further discussion of assumptions met to conduct a multiple regression).

Results

Child illness-specific information

Illness-specific information for all 33 children/adolescents is summarised in table 2.

Parents/carers of 84.8% of the sample identified the type of encephalitis that their child contracted. Most children were reported to have received acyclovir treatment at the time of their illness, though 45.5% of parents/carers were unsure how long their child had received this. Nearly half of the children/adolescents had been diagnosed with epilepsy, and over half reported chronic health concerns following encephalitis (66.7%). Sleep problems following encephalitis were reported for over half of children (see extended results 2.4. for further discussion of demographic/illness specific information).

Table 2. Child Illness Specific Information

	<i>n</i>	%
<i>Type of encephalitis</i>		
Infectious encephalitis (e.g.HSE)	18	54.5
Post acute encephalitis (e.g ADEM)	9	27.3
Other type	1	3
Unknown origin	3	9.1
Not sure	2	6.1

<i>Acyclovir treatment</i>		
Yes	25	75.8
No	4	12.1
Not sure	4	12.1
<i>Length of treatment</i>		
Less than 14 days	8	24.2
14 – 20 days	2	6.1
21 days or over	4	12.1
Not sure	15	45.5
No Acyclovir treatment	4	12.1
<i>Diagnosis of epilepsy since illness</i>	16	48.5
<i>Pre-morbid conditions</i>	7	21.2
<i>Chronic health conditions post-encephalitis</i>	22	66.7
<i>Sleep difficulties post-encephalitis</i>	21	63.6

Test results

*PedsQL*TM - The mean total health score was 48.71 (SD = 23.42). Scores were spread between 0 and 89, with 0 indicating the lowest possible score. The physical total health score was higher overall for the sample (M = 56.25; SD = 29.99) than the psychosocial health score (M = 43.88; SD = 22.32). The summary scores also show large variation with physical health scores ranging from 0 - 100, and psychosocial health scores ranging from 0 – 87.

CMQ – The mean total CMQ score was 141.27 (SD = 56.69). The spread of scores was between 34 and 238, with the maximum score on this measure being 238.

BRIEF – The overall mean for the GEC was 71.64 (SD = 13.03) with scores ranging between 38 and 97. A mean score of 71.97 (SD = 15.74) with scores ranging between 41 and 102 was found for the BRI and a mean of 68.67 (SD = 11.40), with a range of 38 -87 for the MI. The mean scores for BRI, MI and the GEC were all above 65, indicating clinically significant impairment (Gioia et al., 2000).

Hypothesis 1 - A statistically significant relationship will be observed between parent/carer reported executive function impairment and parent/carer reported HRQL in children and adolescents post-encephalitis.

The GEC was significantly negatively correlated with the PedsQL™ total health score ($r_s(33) = -.74, p < .001$), supporting experimental hypothesis 1. The direction of this correlation indicated a relationship where as parent/carer reported executive function impairment increased scores of parent/carer reported HRQL decreased.

Hypothesis 2 - A statistically significant relationship will be observed between parent/carer reported everyday memory problems and parent/carer reported HRQL in children and adolescents post-encephalitis.

The CMQ score was significantly negatively correlated with the total health

score of the PedsQL™ ($r(33) = -.77, p < .001$), supporting experimental hypothesis 2. The direction of this correlation indicates a relationship where as parent/carer reported everyday memory problems increased parent/carer reported HRQL decreased.

(See extended results 2.5. for further correlational analysis of subscale scores).

Additional exploratory analyses

Further to the primary hypotheses additional explorations were conducted to consider whether any of the demographic/illness specific factors had a relationship with the PedsQL™ measure of HRQL. Due to missing data or parents/carers being unsure of specific details regarding their child's encephalitic illness, age at onset of illness, diagnosis of epilepsy and sleep difficulties were the only variables that could be investigated alongside the PedsQL™. Neither age at onset of illness ($r_s(33) = .06, ns$) or diagnosis of epilepsy ($r_{pb}(33) = .30, ns$) correlated significantly with the PedsQL™ total health score. However, sleep difficulties was found to significantly correlate with the PedsQL™ total health score ($r_{pb}(33) = .52, p < .002$). This was in the direction that parent/carer report of no sleep difficulties was significantly related to higher parent/carer ratings of the PedsQL™ total health score (see extended results 2.6 for further details of exploratory correlational analyses of subscale scores).

Multiple linear regression

A multiple linear regression was conducted with variables that correlated significantly with the PedsQL™ total health score.

Table 3. Variables correlating significantly with the PedsQL™

	PedsQL™
CMQ	-.77*
GEC	-.74*
Sleep difficulties	.52**

Note: * $p < 0.001$ ** $p < 0.002$

Sleep difficulties, and the CMQ and GEC were entered into a multiple linear regression with the total health score of the PedsQL™. Due to no prior research investigating HRQL of children/adolescents post-encephalitis, a forced entry multiple linear regression was utilised.

The regression model is significant at the $p < 0.001$ level, and sleep difficulties and the GEC and CMQ combined are found to account for up to 71% of the variance of the PedsQL™ total health score. Whilst the overall regression model is statistically significant, the variable of sleep difficulties is not found to

contribute in a statistically significant way. The GEC and CMQ score are both found to contribute significantly, with the CMQ score being the most statistically significant predictor (see extended results 2.7 for assumptions met for conducting a multiple regression).

Table 4. Multiple Linear Regression between sleep difficulties, the CMQ and GEC of the BRIEF, and the PedsQL™ Total Health Score

Model	Unstandardized Coefficients		Standardized Coefficients	<i>t</i>	Sig.
	B	Std error	Beta		
(Constant)	108.03	21.64		4.99	.000
Sleep difficulties	8.75	5.64	.18	1.55	.132
CMQ	-.18	.06	-.44**	-2.90	.007
GEC	-.63	.30	-.35*	-2.09	.045

Note: $R^2 = .71$ ($p < 0.001$). * $p < 0.05$ ** $p < 0.01$

Discussion

The findings of this study support the prediction of statistically significant relationships between everyday memory, executive function, and parent/carer reported HRQL of children post-encephalitis. More specifically, the results show a significant negative correlation with increased parent/carer reports of everyday memory problems and executive function impairment being related to lower parent/carer reported HRQL in this clinical population.

The findings of this study are consistent with previous research which has found memory problems and executive function impairments to be present for children post-encephalitis (Dowell et al., 2001; Kneen & Solomon, 2007; McGrath et al., 1997). It has also indicated low scores of parent/carer reported HRQL for this clinical population, a pattern which has been identified in children with other neurological conditions such as epilepsy (Ronen et al., 2003), ADHD (Klassen et al., 2004), and TBI (Souza et al., 2007; Stancin et al., 2002). The finding of a significant association between executive function and HRQL is also consistent with the findings of Sherman et al. (2006) who identified a significant relationship between executive function and HRQL in children with epilepsy (see extended discussion 3.1. for further discussion on everyday memory, executive function and HRQL).

This study provides some insight into relationships that appear to exist with parent/carer reported HRQL and the most frequently reported neuropsychological consequences of encephalitis in children. As a correlational design these findings do not present causality and therefore the influence of third variables must be considered. Missing data and a small sample size made further planned exploratory analyses relating to illness specific factors problematic. The variables of age at time of illness, diagnosis of epilepsy and sleep difficulties were explored, with sleep difficulties being found to correlate significantly with parent/carer reported HRQL. The finding of a significant relationship between sleep and parent/carer reported HRQL is consistent with existing literature regarding children's sleep problems and HRQL (Mitchell & Kelly, 2008). The finding of no relationship between age at onset of illness, diagnosis of epilepsy and parent/carer reported HRQL is not consistent with previous literature that has found reduced HRQL in children with epilepsy (Ronen et al., 2003) or with literature of the outcome of brain injury at different ages (Dowell et al., 2001; Rautonen et al., 1991). Due to the exploratory nature of this study, it is uncertain whether these findings are specific to this clinical population. Further research with larger sample sizes and more specific and sensitive measurement of these variables is required. Future research could investigate further variables of interest such as type of encephalitis, and timely diagnosis, initiation and length of time of treatment with acyclovir which have been identified in the literature as significant when determining outcome for children (Elbers et al., 2007; Marton et al., 1996;

McGrath et al., 1997; Tunkel et al., 2008; Whitley & Gnann, 2002). (See extended discussion 3.2. for further discussion on exploratory findings).

Combined, parent/carer reported everyday memory, executive function and sleep difficulties accounted for up to 71% of the variance in parent/carer reported HRQL. Whilst everyday memory and executive function contributed significantly to the model, everyday memory was found to be the most statistically significant predictor.

The findings of this study have a number of clinical implications. Understanding the problems that parent/carers report their children experience with everyday memory, executive function and sleep following encephalitis, helps identify specific areas for support and rehabilitation. Everyday memory, executive function and sleep can have a significant impact on a child's learning and development, both in educational and social domains. The finding of a relationship between these parent/carer reported difficulties and reduced HRQL is important, with implications for a child's development and family relationships. Therefore, treatment and rehabilitation should be targeted towards helping parents/carers, and their children, to manage these difficulties and aid a child's learning and development in the home and school environment. An alternative interpretation of low parent-reported HRQL is that parents underestimate their child's HRQL based on their own interpretations, or the distress and pressure of caring for their child. Further research to consider

and investigate the child's own self-report of HRQL would help to investigate this further.

The significant relationships found between parent/carer reported neuropsychological impairments and HRQL following encephalitis suggests that wide ranging support and assessment is imperative. It is not known how many participants will have had neuropsychological assessment, although the findings would suggest that assessment in these domains is important given their identified relationship with parent/carer reported HRQL. Neuropsychological impairments may be less explicit following illness than are other neurological or health related consequences such as sleep, epilepsy or motor impairment. However, their stronger relationship with parent/carer reported HRQL may demonstrate how pervasive these difficulties can be for a young person in contrast to consequences such as epilepsy which may be more discrete, particularly if the epilepsy is well controlled. Therefore, neuropsychological assessment to help identify and monitor difficulties would be advantageous and finds further support in the literature (Starza-Smith et al., 2007). The significant relationships between parent/carer reported everyday memory and executive function impairments, and parent/carer reported HRQL, would suggest that identifying difficulties and supporting children and families through strategies and rehabilitation techniques to aid a child's recovery in these areas may in turn help to improve their HRQL. The importance of neuropsychological assessment and rehabilitation in these areas should be

made explicit to families and professionals following encephalitis in childhood. This is particularly important as rehabilitation services for children in the UK are found to be limited (Crouchman, 1998; Hawley, Ward, Magney & Long, 2002) and in most cases rehabilitation is conducted through recommendations to home and school (Walker & Wicks, 2005) See extended discussion 3.3 for further discussion of clinical implications).

Limitations to this study must be considered. Whilst invitation through a national charity aimed to increase recruitment across a wide geographical area, the representativeness of this sample may have been compromised by a small response rate and bias based on self-referral to the Encephalitis Society. The response rate may have presented a bias whereby those with children/adolescents experiencing more difficulties, or those with fewer difficulties, may have been more likely to respond. Caution in the generalisation of these findings should therefore be taken with the impact of non-response bias highlighted in the literature (Edwards et al., 2002; MacDonald, Newburn-Cook, Schopfacher & Richter, 2009). In addition, collection of more detailed demographic and illness-specific information may have provided greater scope for investigation. For example, respondent relationship to child and more detailed information regarding the child's illness. (See extended discussion 3.4 and 3.5 for further consideration of study limitations and strengths).

Encephalitis in childhood remains an under-researched topic area which would benefit from much further research. Larger studies with greater sample sizes, allowing for multiple comparisons, and control samples, would be advantageous. With 71% of the variance of parent/carer reported HRQL accounted for in this study, a greater sample size could allow for further investigation of more potential predictor variables. Research looking at child self-report, and possible concordance with parent/carer report, would be advised, as well as qualitative research to explore in more detail aspects of life for children/adolescents and their families post-encephalitis. (See extended discussion 3.6. for further discussion of recommendations for future research).

The findings of this study contribute to the literature in assessing parent/carer reported HRQL in children, and specifically to the limited evidence base regarding encephalitis in childhood. This study has indicated that relationships exist between parent/carer reported HRQL and parent/carer reported problems of everyday memory, executive function and sleep following encephalitis in childhood. This has raised implications for clinical practice and recommendations for future research. (See extended discussion 3.7 for critical reflection on research and philosophy of science).

(Journal paper word count including directions to extended paper = 5388)

(Journal paper word count excluding statements = 5000)

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Appendix A

Guidance for authors for British Journal of Clinical Psychology

<http://www.bpsjournals.co.uk/journals/bjcp/notes-for-contributors.cfm>

The British Journal of Clinical Psychology publishes original contributions to scientific knowledge in clinical psychology. This includes descriptive comparisons, as well as studies of the assessment, aetiology and treatment of people with a wide range of psychological problems in all age groups and settings. The level of analysis of studies ranges from biological influences on individual behaviour through to studies of psychological interventions and treatments on individuals, dyads, families and groups, to investigations of the relationships between explicitly social and psychological levels of analysis.

The following types of paper are invited:

- Papers reporting original empirical investigations
- Theoretical papers, provided that these are sufficiently related to the empirical data
- Review articles which need not be exhaustive but which should give an interpretation of the state of the research in a given field and, where appropriate, identify its clinical implications
- Brief reports and comments

Circulation

The circulation of the Journal is worldwide. Papers are invited and encouraged from authors throughout the world.

Length

Papers should normally be no more than 5000 words, although the Editor retains discretion to publish papers beyond this length in cases where the clear and concise expression of the scientific content requires greater length.

Submission and reviewing

All manuscripts must be submitted via our [online peer review system](#). The Journal operates a policy of anonymous peer review.

Manuscript requirements

- Contributions must be typed in double spacing with wide margins. All sheets must be numbered.
- Tables should be typed in double spacing, each on a separate page with a self-explanatory title. Tables should be comprehensible without reference to the text. They should be placed at the end of the manuscript with their approximate locations indicated in the text.
- Figures can be included at the end of the document or attached as separate files, carefully labelled in initial capital/lower case lettering with symbols in a form consistent with text use. Unnecessary background

patterns, lines and shading should be avoided. Captions should be listed on a separate sheet. The resolution of digital images must be at least 300 dpi.

- For articles containing original scientific research, a structured abstract of up to 250 words should be included with the headings: Objectives, Design, Methods, Results, Conclusions. Review articles should use these headings: Purpose, Methods, Results, Conclusions. Please see the document below for further details:

Structured abstracts

Authors should note that all papers submitted to the British Journal of Clinical Psychology must include structured abstracts. Papers will not be considered for publication unless they have a structured abstract in the correct format.

Articles containing original scientific research should include a structured abstract with the following headings and information:

Objectives State the primary objectives of the paper and the major hypothesis tested (if appropriate).

Design Describe the design of the study and describe the principal reasoning for the procedures adopted.

Methods State the procedures used, including the selection and numbers of participants, the interventions or experimental manipulations, and the primary outcome measures.

Results State the main results of the study. Numerical data may be included but should be kept to a minimum.

Conclusions State the conclusions that can be drawn from the data provided and their clinical implications (if appropriate).

- For reference citations, please use APA style. Particular care should be taken to ensure that references are accurate and complete. Give all journal titles in full.
- SI units must be used for all measurements, rounded off to practical values if appropriate, with the imperial equivalent in parentheses.
- In normal circumstances, effect size should be incorporated.
- Authors are requested to avoid the use of sexist language.
- Authors are responsible for acquiring written permission to publish lengthy quotations, illustrations, etc. for which they do not own copyright.

For guidelines on editorial style, please consult the APA Publication Manual published by the American Psychological Association.

Brief reports and comments

These allow publication of research studies and theoretical, critical or review comments with an essential contribution to make. They should be limited to 2000 words, including references. The abstract should not exceed 120 words and should be structured under these headings: Objective, Method, Results, Conclusions. There should be no more than one table or figure, which should only be included if it conveys information more efficiently than the text. Title, author name and address are not included in the word limit.

Publication ethics

All submissions should follow the ethical submission guidelines outlined in the: Ethical Publishing Principles – A Guideline for Authors Code of Ethics and Conduct (2006)

Supplementary data

Supplementary data too extensive for publication may be deposited with the British Library Document Supply Centre. Such material includes numerical data, computer programs, fuller details of case studies and experimental techniques. The material should be submitted to the Editor together with the article, for simultaneous refereeing.

Copyright

On acceptance of a paper submitted to a journal, authors will be requested to sign an appropriate assignment of copyright form. To find out more, please see our Copyright Information for Authors.

Appendix B

NHS Research Ethical Approval Letter



National Research Ethics Service Leicestershire, Northamptonshire & Rutland Research Ethics Committee 2

1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 8839428
Facsimile: 0115 9123300

23 February 2009

Miss Emily Talbot
Trainee Clinical Psychologist
University of Lincoln
Trent Clinical Psychology Doctorate Course
Court 11, Satellite Building 8, University of Lincoln
Brayford Pool, Lincoln
LN6 7TS

Dear Miss Talbot,

Full title of study: Health-related quality of life (HRQL) of children and adolescents following encephalitis
REC reference number: 09/H0402/6

Thank you for your letter of 12 February 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA). The favourable opinion for the study applies to all sites involved in the research. There is no requirement for other Local Research Ethics Committees to be informed or SSA to be carried out at each site.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority.
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Indemnity / Insurance		13 August 2008
Assent Form for Children / Adolescents	1	05 November 2008
Questionnaire: BRIEF		
Questionnaire: Children's Memory Questionnaire		
Questionnaire: Demographic / illness specific questionnaire	1	05 November 2008
Questionnaire: PedsQL - ages 13-18	4.0	
Questionnaire: PedsQL - ages 8-12	4.0	
Peer Review		18 December 2008
Letter from Sponsor		19 December 2008
Protocol	1	05 November 2008
Investigator CV	Chief Investigator	20 December 2008
Application	AB/133013/1	30 December 2008
Letter of invitation to participant - Encephalitis Society	1	05 November 2008
Investigator CV	Educational Supervisor	27 November 2008
Response to Request for Further Information		12 February 2009
Participant Consent Form	2	29 January 2009
Participant Information Sheet: Child (8-10 years)	2	29 January 2009
Participant Information Sheet: Child/Adolescent (11-15 years)	2	29 January 2009
Participant Information Sheet: Parent/Carer	2	29 January 2009
Letter of invitation to participant - NUH	2	29 January 2009
Covering Letter		12 February 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review –guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0402/6

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely,



Mr Ken Willis / Miss Jeannie McKie
Chair / Committee Coordinator

Email: jeannie.mckie@nottspct.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Dr Mark Gresswell - University of Lincoln
R&D office for NHS care organisation at lead site - NUH (via email)

Appendix C

Email response to request for University of Lincoln ethical approval letter

Dear Emily,

This is to confirm that you received ethical approval for your project “Health-related quality of life (HRQL) of children and adolescents following encephalitis” on 23-3-09 from the School of Psychology’s Ethics Committee. All my best,
Emile

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Extended paper

1. Extended background

1.1. Causative agents leading to encephalitis

Granerod and Crowcroft (2007) identify that infection of the central nervous system is the most common cause of encephalitis and detail more than 100 different pathogens that have been recognised as causative agents. The most commonly seen viral agents in England are the herpes viruses, such as herpes simplex virus (HSV) and varicella zoster virus (VZV) (Davison, Crowcroft, Ramsay, Brown & Andrews, 2003). In other countries different agents such as those transmitted by vectors or animals are more prominent, for example in China, Southeast Asia and India the Japanese encephalitis virus, transmitted via mosquitoes, is more frequently seen (Granerod & Crowcroft, 2007). In a study by Glaser et al. (2003), in which they investigated the diagnosis of aetiological agents in a sample of 334 patients who had encephalitis, they found that for 62% of the sample the aetiology of the illness remained unknown, despite thorough exploration.

1.2. Worldwide incidence of encephalitis

Incidence varies across the world with Johnson (1996) reporting worldwide incidence figures between 3.5 and 7.4 per 100,000 across the ages, and 16 per 100,000 in children. Comparing the incidence rates in individual countries across the world is seen as challenging due to the wide variations in factors such as vaccine procedures, different definitions of encephalitis and the varying causative agents (Granerod & Crowcroft, 2007). For example, Rantala and Uhari (1989) found, in a study of childhood encephalitis in Finland, when looking at cases of childhood encephalitis between the years of 1973 and 1987, there were no cases of encephalitis caused by measles, mumps or rubella after 1982, when a vaccine had been introduced to protect against these viruses.

Whilst comparing the specific incidence in individual countries is problematic, it can be seen from the figures detailed that across the world there is a higher incidence of encephalitis in infancy and childhood.

1.3 Treatment and outcome with acyclovir

Acyclovir is identified as the anti-viral treatment of choice for encephalitis caused by the herpesviruses, particularly herpes simplex virus encephalitis (HSE) (Skoldenberg et al., 1984; Whitley et al., 1986). However, acyclovir is limited to targeting this group of viruses, and specific antiviral treatments are

less well established for encephalitis caused by other non-herpes viruses (Tunkel et al., 2008). Other treatments that may be prescribed include anti-convulsants for the management of seizures, steroids to reduce swelling, and antibiotics that whilst not specifically targeting the causative virus, may prevent further illness by controlling bacterial infection (Encephalitis Society, 2005).

Acyclovir, for HSE, and earlier detection and diagnosis of the condition, as a result of advancing medicine, has assisted in reducing mortality (McGrath, Anderson, Croxson, & Powell, 1997; Skoldenberg et al., 1984; Whitley et al., 1986). It has been identified that individuals who have contracted encephalitis under the age of 30, and had a Glasgow Coma Scale score over 10, are found to experience the best outcome with acyclovir treatment (Whitley et al., 1986). However, encephalitis can lead to a range of neurological and neuropsychological sequelae (Benjamin et al., 2007; Dowell, Easton & Solomon, 2001; Hooper, Williams, Wall & Chua, 2007; McGrath et al., 1997; Smyth, Ozanne & Woodhouse, 1990; Van-Schoor, Naude, van-Rensburg, Pretorius & Boon, 2005; Whitley, 2006).

In a review of the literature, McGrath et al. (1997) highlighted that, prior to anti-viral treatment being available, the mortality rate for those with HSE was approximately 70%, with the surviving 30% experiencing severe neurological deficits. Within this paper they went on to publish a more up to date study of individuals with HSE who were treated with acyclovir. In a study of 42 patients

post-encephalitis ranging from three months to 91 years old at presentation, they found that with anti-viral treatment 30% of the sample died or experienced severe neurological deficits, and whilst the remaining 70% of survivors recovered to the extent that they could be independent in activities of daily living, most experienced neurological symptoms and/or signs. They identified that the most common sequelae of the survivors were memory impairments (69%), personality and behavioural abnormalities (45%), and epilepsy (24%). While this paper clearly portrays the reduction in mortality due to advancing medicine, alongside the potential consequences of surviving encephalitis, it does not clearly differentiate between those who contracted encephalitis in childhood and those in adulthood.

A published study that has addressed childhood encephalitis specifically is that by Elbers et al. (2007), who published a 12 year prospective study of childhood HSE. They found that 63% of the sample of children that they studied developed adverse neurological outcomes such as epilepsy, developmental delay and hemiplegia. On further investigation they discovered that 71% of the children who had contracted HSE and been treated with acyclovir prior to 1999, when the recommended length of anti-viral treatment was 14 days, had adverse neurological outcomes, as opposed to 55% of the children who were treated after 1999, when the recommended length of treatment was increased to 21 days. This appears to have been a robust longitudinal study including all children admitted to hospital with acute HSE between 1994 and 2005.

In addition to the length of time of treatment, it has been reported that survival rates are found to be improved if treatment is initiated within four days of the onset of the illness (Marton, Gotlieb-Steimatsky, Klein & Arlazoroff, 1996; Whitley & Gnann, 2002). Therefore, early diagnosis and treatment with acyclovir, for HSE, are critical for preventing death and minimising long-term disability. Important investigations for diagnosis include, investigation of cerebrospinal fluid (CSF) through lumbar puncture; computed tomography (CT) and magnetic resonance imaging (MRI) of the brain; electroencephalogram (EEG) to monitor brain activity; and blood tests to exclude metabolic encephalopathy (Encephalitis Society, 2005; Stone & Hawkins, 2007). Fortunately earlier diagnosis of the condition has been greatly aided by the advancement and development of technology and neuro-imaging (Lahat et al., 1999).

Tunkel et al. (2008) have recently published the 'Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) on the Management of Encephalitis'. These guidelines identify that acyclovir should be initiated as soon as possible in all patients with suspected encephalitis, while the results of additional diagnostic examinations are waited for. They also consider that whilst in many cases of encephalitis the aetiology remains unknown, identification of the specific causative agent is important when considering factors such as prognosis, counselling for patients and families and potential public health

interventions. These guidelines were prepared by an expert panel from the IDSA who reviewed literature available on the diagnosis and management of encephalitis, from articles and research published since 1996. A limitation to this literature review was that, due to the lack of randomised controlled trials (RCTs) on the diagnosis and management of encephalitis, the panel were reliant on recommendations made from research based on single case reports and small samples. However, given the lack of RCTs in this topic area this is not a limitation that is easily corrected unless further research is conducted. These guidelines were developed by experts on infectious diseases in paediatric and adult populations and therefore provide up to date and comprehensive reviews and guidance for the diagnosis and management of encephalitis across the life span.

1.4. Differences in childhood and adulthood encephalitis

Dowell et al. (2001) from the UK Encephalitis Society conducted a postal survey in which they received responses from 139 individuals who had contracted encephalitis as children. They found that, of those who responded, 72% had not been able to 'fully resume their normal life' and 53% were eligible for Disability Living Allowance (DLA). They identified that 24% of the respondents had received a diagnosis of HSE. This survey also provided an exploration of the variations in consequences for children and adults post-encephalitis, with the Encephalitis Society receiving responses from a further

261 individuals who contracted encephalitis as an adult. They identified that children were more likely to report difficulties with fine motor skills, and where adults reported experiencing more anxiety and depression, children reported mood swings. Dowell et al. (2001) also found that children were twice as likely as adults to develop epilepsy following encephalitis. Educational factors were clearly identified as significant for those individuals who contracted encephalitis as children. They found that 44% of respondents had a statement of special educational needs or were attending a school for children with special educational needs, 60% reported difficulties with new learning and 72% with difficulties in concentration and attention.

This study provided information about the consequences of encephalitis from individuals who had contracted the condition across the life span. This enables comparison of outcome following child-onset and adult-onset encephalitis. The study also provides data on encephalitis caused by HSV as well as encephalitis that is non-HSE. This is an advantage, as research investigating non-HSE is less reported in the literature. However, the study did rely on a self-report postal survey which can demonstrate some disadvantages to face-to-face interviews due to uncertainties regarding who completed the questionnaire, and other identified challenges to self-report such as poorer response rates, motivation of respondents, and ability to check responses if answers are unclear (Clark-Carter, 1997). Whilst these factors must be considered when interpreting the results of this survey, it is observed that a good response rate was obtained in

the study and similar findings are apparent in the literature within this topic area.

A case study published by Benjamin et al. (2007) detailed the pre-and post-neuropsychological profile of a seven year old child with non-HSV encephalitis, possibly caused by Mycoplasma pneumonia. This case study is unique in a number of ways as it is a non-HSE case, and as a pre-encephalitis neuropsychological assessment had been conducted with the child seven months prior to the illness. In most cases pre-morbid functioning would have to be estimated from information such as developmental history and prior school attainment. In formal post-encephalitis assessment, Benjamin et al. (2007) found significant difficulties in language and verbal expression, attention and speed of processing, and executive and memory difficulties. They concluded that the neuropsychological changes reflected the damage evident on MRI, such as bilateral inferior frontal, temporal and some parietal damage. This study confirms the findings of other studies that indicate specific frontal and temporal damage and neuropsychological consequences including executive function and memory difficulties, post-encephalitis. Whilst it must be noted that these findings are based on a single case design, the strength of this study is in the investigation of a non-HSE case, and the advantage of having pre-encephalitis neuropsychological assessment results.

1.5. Sequelae following encephalitis

Memory and encephalitis

McGrath et al. (1997) carried out a study in which they investigated the diagnosis and long-term outcome of encephalitis, in a sample of 42 patients treated with acyclovir for HSE. This sample included individuals aged between three months and 91 years. They found that 69% of the sample demonstrated symptoms of memory impairment and 70% short-term memory problems, indicating memory difficulties as a consequence post-encephalitis. It is important to consider, however, the means of assessment of these impairments. The cognitive measures used to assess memory and short-term memory impairment included the mini-mental state examination and an un-standardised task in which participants were requested to memorise and recall a list of five items after five minutes. These are brief memory tests and do not provide a detailed analysis of these difficulties. However, Pewter, Williams, Haslam and Kay (2007), who carried out a study in which they conducted comprehensive neuropsychological assessments with adults post-encephalitis, also found impairments in memory, particularly, autobiographical memory, semantic memory and working memory.

Key case studies in the literature have also demonstrated severe anterograde amnesia in cases of HSE in childhood (Benedict, Shapiro, Duffner, & Jaeger,

1998; Wood, Brown, & Felton, 1989), and Dowell et al. (2001) found that 40% of their respondents who contracted encephalitis as children reported difficulties with long-term memory, and 44% with short-term memory difficulties. In a paper on the management and outcome of viral encephalitis in children, Kneen and Solomon (2007) highlight that neurocognitive impairments such as changes in memory are common after viral encephalitis and indicate that difficulties can be found in re-integrating back to school due to these problems.

Executive function and encephalitis

Hokkanen and Launes (2007) detail impairment to executive function following HSE. They define executive function as enabling “a person to engage in purposeful actions and carry them out logically” (Hokkanen & Launes, 2007, p. 459). They identify behavioural problems that can result from executive function impairment, including impulsivity, planning difficulties, perseveration of action, difficulty making shifts in attention, and emotional flattening or lability. The frontal and orbito-frontal regions of the brain are found to be closely associated with executive function impairments and Hokkanen and Launes (2007) identify that HSE can often result in extended damage to the orbito-frontal regions of the brain. Whilst this article is a useful review of the literature and the consequences that are possible following encephalitis, the focus of this article is on HSE, and does not identify child and adult populations individually.

Schmolck, Maritz, Kletzin, and Korinthenberg (2005) have found that children, following tick-borne encephalitis, are more likely to have impairments on tests of attention and psychomotor speed than controls. A further study by Hooper et al. (2007) has looked at caregiver stress, coping and parenting styles in 36 cases of childhood encephalitis. They divided their sample into two experimental groups, those children who had experienced encephalitis more than seven years ago, termed the 'remote' group, and those who had experienced encephalitis within the last seven years, the 'recent' group. Hooper et al. (2007) found very high levels of dysexecutive problems in their sample, with no significant differences between the 'remote' and 'recent' group, indicating that dysexecutive syndrome is a persistent difficulty over time. They also concluded support for their prediction that high levels of child dysexecutive function would correlate with high levels of parental distress. This indicates that executive function problems are a considerable difficulty post-encephalitis for children and can have significant implications for their families. Hooper et al. (2007) acknowledge that caution is needed when interpreting these results due to the small sample size and indicate that larger scale studies are warranted. However, the study provides an exploration of this topic area and provides further evidence of difficulties faced by children, and their families, post-encephalitis.

In addition to highlighting difficulties with memory, Kneen and Solomon (2007) also detail common problems in perception and executive function skills, such

as organising and planning, in children post-encephalitis. They further indicate that this can create challenges for children when trying to reintegrate back to school.

Research over recent years has highlighted the findings of neuroimaging and cognitive studies that have found that the pre-frontal cortex of the brain continues to undergo development, such as myelination of neurons and synaptic pruning, throughout late childhood, adolescence and into early adulthood (Blakemore & Choudhury, 2006). Research has identified that different executive functions may have different developmental trajectories as suggested by children's performance on executive function tasks at different points during childhood and adolescence (Anderson, Anderson, Northam, Jacobs & Catroppa, 2001), and it is speculated that these differences may be due to the pruning and myelination processes that are occurring in the frontal cortex during a child's adolescent years. These findings could indicate the potential impact of frontal brain damage during childhood on the developmental trajectory of a child's executive functions.

Neurological problems and encephalitis

As discussed earlier, research has indicated significant neurological outcomes following encephalitis in childhood. For example, Dowell et al. (2001) found that children were twice as likely to contract epilepsy than adults. Schmolck et al.

(2005) also found slower background activity, particularly of alpha activity, in EEGs of children with tick-borne encephalitis compared to healthy controls. Kolski et al. (1998) report on the findings of Klein, Hom, Anderson, Latrizza & Toltzis (1994), that neurological status at discharge has been found to be a significant diagnostic predictor of outcome, and found in their own study of 50 children with acute encephalitis, that 67% had evidence of neurological impairment at time of discharge. They also identified that only 40% of their sample had confirmed or probable aetiological agents identified as the cause of the encephalitis, suggesting that for 60% the aetiology of the illness remained unknown.

The psycho-social impact of encephalitis

In an article aimed at raising awareness of encephalitis in 2006, Easton and Atkin acknowledged that whilst research had been conducted looking at medical aspects of the condition, there was limited literature and research specifically regarding the psycho-social consequences of encephalitis. Following this, a study carried out by Pewter et al. (2007), within a population of adults with encephalitis, found a relationship between depression and interpersonal anxiety and cognitive functions. Research has also been conducted that has seen the impact of childhood encephalitis, and its consequences such as executive function difficulties, on parental distress, coping and parenting styles (Hooper et al., 2007).

An indication of the psycho-social impact of encephalitis on children and adolescents is evident in the postal survey carried out by Dowell et al. (2001). They found that difficulties reported by those who contracted encephalitis as children included tiredness/fatigue (68%), mood swings (66%), anxiety (55%), frustration/anger (65%) and concentration/attention (72%). Although the limitations of a postal survey must be considered when relying on these findings they provide a good indication of the types of difficulties that are reported by those individuals who have contracted encephalitis as children.

Other than this study, the majority of research conducted looking at psycho-social consequences of encephalitis is specific to the adult population, or to the impact on the family surrounding the child. There is little research looking specifically at the child/adolescent directly or at health-related quality of life (HRQL) for these individuals post-encephalitis.

1.6. Assessing HRQL in children

Quality of life (QoL) has been defined as incorporating an individual's well-being in psychological, social, occupational and educational domains (Duncan, 1990). Health-related quality of life (HRQL) has been described as specifically referring to the impact of health and illness on an individual's QoL (Eiser & Morse, 2001a) and follows the World Health Organisation's definition of health as 'the state of complete physical, mental and social wellbeing and not merely the

absence of disease or infirmity'. With a greater proportion of children surviving serious and complicated health conditions due to advances in medicine and surgical intervention, HRQL is becoming an increasingly important concept to consider (Mitchell & Kelly, 2008). The advantages of surviving a potentially fatal condition are considered alongside the short- and long-term consequences and effects of the condition and/or its treatments. It is assumed that treatment in hospital, intrusive medical procedures, queries regarding survival and potential disability are likely to have a negative effect on children (Vincent & Higginson, 2003). Therefore it is considered that in order to fully understand these effects and improve medical and health care for children, it is essential to be able to assess a child's QoL effectively (Vincent & Higginson, 2003). McGee (1994) has highlighted a number of important justifications for assessing QoL in children, such as ethical considerations regarding the impact of a treatment on children, increasing understanding of the impact of a condition between professionals and their patients, developing knowledge to prepare families, professionals and children to the likely difficulties following an illness or treatment and the potential for increasing QoL through highlighting areas of particular concern for children and their families.

Assessing QoL in children has, however, been identified in the literature as challenging due to the implications of the age of the child. For example, Vincent & Higginson (2003) highlight four considerations when looking at assessing QoL in children, the physical development of the child, developing appropriate

concepts of QoL that relate to the child, the child's cognitive development and the specific contents of the measure and its appropriateness to children.

Disease-specific versus generic HRQL measures

A consideration when evaluating and exploring HRQL in children is considering the standards against which the comparisons are being made. Specifically, whether children with a particular condition are being compared with children with the same condition or are being compared with the general population.

Disease-specific measures of HRQL incorporate domains that are related to a specific condition. They are reported to provide maximum content validity and good sensitivity and specificity (Eiser & Morse, 2001a). Deyo and Patrick (1989) have suggested that disease-specific measures allow a clinician better focus on the particular areas of concern and the responsiveness to specific interventions that are being implemented for that particular disease or condition. Despite these advantages some limitations to disease-specific measures can be identified. For example, some children may have co-morbidity, increasing the number of condition-specific measures needed for the child. Additionally, for children with rare conditions a condition-specific measure may not be available and development of a condition-specific one may not be possible due to difficulties in gaining a large enough normative sample in order to establish the psychometric properties (Eiser & Morse, 2001a)

A generic measure allows a child's HRQL to be compared against the normal healthy population. This can be helpful in being able to compare the HRQL of children with a particular condition against the HRQL of those in the general population. Generic measures are developed in order to be applicable across conditions regardless of severity or treatments. Some of the advantages of generic measures are that they are found to have been through more rigorous development incorporating item selection, reliability and validity (Eiser & Morse, 2001a). Their applicability across conditions can be helpful, particularly for those children who have multiple diagnoses. There are identified disadvantages to the generic approach however. For example, some have suggested that whilst these measures are comprehensive, they may not respond as well to the small changes in a child's condition and that they may overlook clinically relevant aspects of a child's life related to their specific condition (Eiser & Morse, 2001a).

Self- versus proxy-report when assessing HRQL in children

There are different methods of obtaining a measure of HRQL for children. One is to ask the child to provide a self-report of their HRQL, another is to obtain a proxy-report, whereby a parent, carer, teacher or health professional may provide an assessment of their perception of the child's HRQL, or a combination of both self- and proxy-report can be used. Difficulties in obtaining a self-report of HRQL can be seen in paediatric populations and for those with

cognitive impairment. For example, children are sometimes seen as unreliable respondents due to their lack of reading, linguistic and cognitive skills (Eiser & Morse, 2001a) and those with cognitive disability may not be able to self-report due to communication and cognitive difficulties (Punjabi, 2008). For these populations a proxy-report measure may be more appropriate. However, Ronen, Streiner, Rosenbaum & the Canadian Pediatric Epilepsy Network (2003) highlight the concerns that have been raised in the literature regarding the accuracy and acceptability of proxy-report, with the proxy-reporter and child not necessarily holding the same views on illness. They present the view that the child should be the primary source of information regarding their HRQL.

Much work has been done to look at concordance between self-report and proxy-report of HRQL. A number of reviews and studies have highlighted generally low to moderate concordance between the two (Cremeens, Eiser & Blades, 2006; White-Koning et al., 2005; White-Koning et al., 2007). It has been observed through the literature that, on average, parents of healthy children tend to report their child's QoL higher than their child does, while parents of children with chronic conditions tend to report their child's QoL lower than the child themselves (White-Koning et al., 2007). In addition to this trend, it has been identified that there is generally higher concordance found between parent-proxy and child self-report on the more objectively evaluated domain of physical HRQL, when compared to more subjectively evaluated domains such as emotional and social functioning (Eiser & Morse, 2001a).

Despite the findings of low to moderate concordance rates, this is not universal and some studies have found moderate to high concordance between self- and proxy-report (Majnemer, Shevell, Law, Poulin & Rosenbaum, 2008; Theunissen et al., 1998; Verrips, Vogels, den Ouden, Pareth & Verloove-Vanhorick, 2000). In addition, it has been identified by Erhart, Ellert, Kurth and Ravens-Sieberer (2009) that parent proxy-reports have demonstrated slightly higher reliability and may therefore be favoured when considering investigation of small sample sizes.

Punjabi (2008) has written of the challenges of investigating HRQL in paediatric populations due to issues regarding age and cognitive development, and highlights that it is imperative to measure the health status of children at all ages in order to further understand the effects of illness. Punjabi (2008) concludes that at times proxy-report may be the only source of information when self-report is not possible due to young age or cognitive disability and suggests that at times this can provide a more reliable and valid report.

HRQL and epilepsy in children

In a review paper concerning HRQL in childhood epilepsy, Ronen, Streiner and Rosenbaum (2003) highlight the necessity to move beyond the goal of controlling seizures with minimal drug side effects, but to also ensure

identification of other important outcome variables for children with epilepsy. They identify that social, psychological, behavioural, educational and cultural dimensions of the child are also factors that affect the lives of children with epilepsy and their close friends and family. Sherman, Slick and Eyrl (2006) report a study that they conducted in which they investigated executive dysfunction as a predictor of poor quality of life in children with epilepsy. They used measures of executive function and HRQL with 121 children at a centre for those with severe epilepsy. They found that executive dysfunction exerted an adverse influence on HRQL in children with epilepsy with clinical-level impairments in executive dysfunction resulting in a two times increase in the likelihood of poor HRQL. These findings suggest that individuals with childhood onset of epilepsy are at an increased risk of poor psycho-social outcomes (Ronen, Streiner & Rosenbaum, 2003), and those with additional executive function difficulties are at an even heightened risk (Sherman et al., 2006).

With children with encephalitis being twice as likely to develop epilepsy as adults, and with executive function difficulties a commonly reported consequence of encephalitis, this could be seen to be a potential risk factor for HRQL in those children post-encephalitis.

HRQL and attention deficit-hyperactivity disorder (ADHD) in children

Klassen, Miller and Fine (2004) published a study in which they recruited 131

children, who had a diagnosis of ADHD, from a specialist ADHD hospital clinic.

Parents/carers of the children were required to complete a questionnaire providing a measure of the child's HRQL and a measure of ADHD symptoms. Klassen et al. (2004) found that ADHD had a significant impact on multiple domains of HRQL. They found that parents reported particular problems in terms of emotional-behavioural role function, behaviour, mental health and self-esteem. They also identified that the problems of children with ADHD had a significant impact on the parents' emotional health, time to meet their own needs, and interfered with family activities and cohesion of the family. They concluded that those with ADHD had substantially lower HRQL than a normative sample and that HRQL tools provide useful and additional information on the life of the child and their families. A weakness that could be identified in this study, however, is that only parent-report measures were used. Therefore the child/adolescent was not asked to give an indication of their view of their own HRQL.

The finding that HRQL is lower in children with ADHD than a normative sample has also been supported in other studies (Bastiaansen, Koot, Ferdinand & Verhulst, 2004; Sawyer et al., 2002). With children post-encephalitis being found to demonstrate some similar difficulties to those with ADHD, such as difficulties with attention and concentration (Dowell et al., 2001) and executive function difficulties, they may also be at risk of reduced HRQL.

HRQL and traumatic brain injury (TBI) in children

Stancin et al. (2002) carried out a study in order to establish the nature and predictors of HRQL in children with moderate to severe TBI an average of four years post-injury. Stancin et al. (2002) included in their study 42 children with severe TBI, 42 children with moderate TBI and a control sample of 50 children with orthopaedic injuries only. An advantage to this study was that they obtained both parent report and self-report from the child/adolescent, and used a comparative control group. They obtained measures of HRQL and a measure of the child's adaptive behaviour. Stancin et al. (2002) found that, based on parent report, adolescents who sustained severe TBI had a lower HRQL related to overall psychosocial functioning and in the domains of behaviour, mental health, general health, and family impact, than did adolescents with orthopaedic injuries.

One of the central findings in this study was that the adolescents with severe TBI themselves did not indicate a different HRQL to orthopaedic controls. This therefore suggests that adolescents and their parents have different perceptions on HRQL, with parents rating their child's HRQL as lower than the adolescent rated themselves. Stancin et al. (2002) highlight varying hypotheses for this outcome. One is that this finding is suggestive that adolescents may be more prone to minimising concerns about their own health and function. An alternative perspective on this outcome is that the cognitive and behavioural

consequences of severe TBI render the adolescent less capable of accurately appraising their HRQL. This is an important consideration in the area of acquired brain injury where deficits in self-awareness can be common sequelae of severe brain injury and the finding that children/adolescents with TBI indicate lower HRQL has been supported in other research (Souza, Braga, Filho, & Dellatolas, 2007).

Whilst children following TBI can be a heterogenous group due to differences in the severity and location of brain injury, the psycho-social and acquired brain injury factors may relate in a similar way to those children post-encephalitis. It would therefore be predicted that a number of the factors that impact on the HRQL of children/adolescents post-TBI, may also impact on children/adolescents post-encephalitis.

Sleep problems and HRQL

An important consideration when investigating the HRQL of children post-encephalitis is sleep. It is documented that sleep difficulties are a frequently reported problem post-encephalitis (Encephalitis Society, 2005). The Encephalitis Society (2005) advise parents/carers that sleep disorders may be apparent following encephalitis due to disruption in a child's routine whilst staying in hospital, as well effects of inflammation to the brain that are known to disrupt a child's chemical clock in the brain. Specific difficulties that are

identified are sleeplessness, sleeping at odd times or sleeping too much. This is not surprising given the literature highlighting sleep difficulties in other clinical populations where there is trauma to the brain (Hawley, Ward, Magnay & Long, 2002).

Much research has been conducted looking at sleep disorders and their relationship with HRQL. For example, Mitchell and Kelly (2008) report on a number of studies looking at HRQL in children with sleep disorders, concluding that sleep disorders are found to have a dramatic effect on the HRQL of children. Their review of the literature is supported by a number of other studies investigating sleep disturbance and HRQL in children, such as a relationship between sleep disturbance in children with nocturnal enuresis and lower scores of HRQL (Ertan et al., 2009) and findings that improved sleep as a result of a reduction of nasal congestion in children with associated allergic rhinitis, led to an improvement in daytime QoL (Mansfield, Diaz, Posey and Flores-Neder, 2004). In addition, a study by Stewart, Glaze, Friedman, O'Brian Smith and Bautista (2005) found that children with obstructive sleep apnea who were treated with adenotonsillectomy demonstrated large and sustained improvements in QoL.

These findings are useful in highlighting the relationship that is found to exist between disturbed sleep and HRQL for children. However, these studies are based on relatively small sample sizes, an average of 27 children being

studied, and are very specific to the conditions or disorders that are being investigated. A study that has been reported with a larger sample size of 80 and looking at a range of sleep disorders is that by Hart, Palermo and Rosen (2005). In their study, they asked carers of children aged 8 – 15 years to complete the Child Health Questionnaire-Parent Form (CHQ-PF50) and the Children's Sleep Habits Questionnaire (CSHQ) in respect of their child. They found that, when compared with a normative sample, carers of a child with a sleep disorder reported poorer scores on the CHQ-PF50. They also identified that there were no significant differences across sleep disorders.

A review of the literature in this topic area has highlighted that a relationship appears to exist between sleep disorders and HRQL in children. As sleep difficulties are frequently reported problems for children post-encephalitis it would be important to consider sleep problems as a variable in any investigation of HRQL in children following encephalitis.

1.7. Inclusion and exclusion criteria

Inclusion criteria were that participants were the parents/carers of children aged 8–15 years who had been diagnosed with encephalitis at some point during childhood. Participants and their children/adolescents were excluded if they were not able to read and understand English, as questionnaires and outcome measures were written in English, and some measures being standardised on

English speaking populations. This criterion was necessary due to recruitment occurring across a wide geographical area, through postal contact, where translation of measures or interpretation would not be possible. The age range of 8 - 15 years was chosen as the main outcome measures to be employed could be used with parents/carers of children/adolescents within this age range and this allowed investigation of children across a range of years through late childhood and adolescence, within a study with a limited budget for recruitment. The age range provided exploration of children across primary and secondary school age, when education encourages children to become more independent in their learning, and the social and emotional aspects of childhood and adolescence can prove challenging, particularly during transition to secondary education. The age range also allowed for parents/carers to be able to give informed consent to provide anonymous information regarding their child's illness.

An important consideration in the decision of the age range was related to stages of cognitive development. The measures that were chosen allowed for consideration of the age range and different developmental stages. The PedsQL™ has a version for children aged 8 – 12 years old and one for teenagers aged 13 – 18 years. These different versions ensure wording is changed in order to match the developmental stages of children at these different ages. Having highlighted research suggesting that development of executive function continues throughout childhood, adolescence and early

adulthood (Blakemore & Choudhury, 2006), it was important to identify an age range and measure that could account for these developmental changes as a child/adolescent grows. The BRIEF allowed for the calculation of T scores from standardised norms from four developmental age groups and by gender of the child.

Due to the rarity of the condition, and in order to maximise recruitment, children were not excluded if they had any co-existing conditions or developmental disorders. However, details of any pre-morbid conditions or developmental difficulties, experienced by the child, were requested from the parents/carers through the demographic/illness-specific questionnaire. Because the consequences of encephalitis are heterogeneous and wide ranging, to exclude those with pre-morbid or co-existing health or developmental conditions would have significantly limited the potential sample size. The broad inclusion criteria could, however, be seen to bring with it complications and limitations with regards to interpreting the outcome data, for example, incorporating potential confounding variables such as visual or hearing impairments. It was therefore important to ensure that parents/carers were asked about any pre-existing or co-existing health concerns so that this could be considered when analysing and interpreting the data.

The inclusion and exclusion criteria were chosen to maximise recruitment and ensure exploration of the wide variation and heterogeneity of this relatively rare

condition. Detailed demographic and illness-specific information was collected from parents/carers in order to help to explore the sample of children/adolescents and consider any relationships in the data.

1.8. The use of parent/carer report

The literature relevant to using proxy-report was reviewed in section 1.6. This review highlighted some of the advantages and disadvantages that are seen in using proxy-report when looking at HRQL in children. There are a number of factors that have contributed to the use of parent/carer report in this study. The study is an exploratory study investigating an under-researched topic area. Due to the relative rarity of the condition it was felt that maximising recruitment to try to achieve a sample that best typified the clinical population would be advantageous. To achieve this, recruitment on a national scale attempting to gain wide variation in neuropsychological and psychological functioning was felt necessary. Therefore, a postal survey and the utilisation of parent/carer report aimed to help in maximising recruitment and ensure minimal inconvenience and time to participants. In addition, it had been considered that proxy-report may be necessary for those children with cognitive impairment where they may have been unable to complete self-report measures themselves (Punjabi, 2008). In a population of children post-encephalitis a number will experience cognitive difficulties and it was not possible to know prior to sending out invitations to what extent children had cognitive impairment. It was considered that

parent/carer proxy-report in this study would enable the most effective means of gaining as large a sample as possible within the financial and logistical constraints of the research.

1.9. Sample size

Priori calculation

Prior to conducting the study a power calculation was utilised in order to estimate a needed sample size. For the primary correlational stage of this study a G*Power: Version 3.0.8 (Erdfelder, Faul & Bucher, 1996) calculation seeking for a medium effect size of 0.3, for a Pearsons r or Spearman's rho correlation (Cohen, 1992), with a two tailed test, an alpha level of 0.05 and power of 0.8 indicated a required sample size of 64. Based on recommendation by Clark-Carter (1997), this was then multiplied by 1.1 in order to get a sample size necessary for a Spearman's rho correlation, resulting in a required sample size of 70. Spearman's rho correlational analysis had been predicted given the clinical population and the possibility of the sample being not normally distributed.

For the secondary multiple regression stage of this study, it was considered that the necessary sample size for a regression would be dependent on the number of variables that correlated significantly with HRQL and was therefore

considered for inclusion in the regression. Initially a G*Power: Version 3.0.8 (Erdfelder et al., 1996) calculation seeking for a medium effect size of 0.15, for a multiple correlation or regression R^2 (Cohen, 1992), an alpha level of 0.05, power of 0.8, and eight potential predictor variables, indicated a needed sample size of 109. This figure was estimated based on the maximum of eight potential predictor variables being included and it was considered that this would be reduced if less predictor variables were utilised in the multiple regression. Whilst this sample size was the aim, further literature regarding necessary sample size and multiple regression was considered. With Stevens (1986) documenting that a minimum of 10 participants per predictor variable is sufficient for conducting a valid multiple regression. This suggests a minimum sample of 80 participants in a multiple regression with eight predictor variables.

On initial approach to the Encephalitis Society they reported that they had 84 families meeting the inclusion criteria on their database. At this time it was therefore considered that further recruitment procedures through additional acute hospital trusts may aid recruitment to enable the needed sample size. On further investigation it was found that 171 children met the inclusion criteria on the Society database and due to financial limitations of the funded study, it was felt recruitment solely through the Encephalitis Society was the most appropriate. This was considered to be a reasonable aim given prior research by the Encephalitis Society. Easton, Atkin & Hare (2007) report on a postal survey conducted through the Society in which a response rate of 55% was

achieved when contacting individuals following encephalitis. This included parents/carers of children after encephalitis. Hooper et al. (2007) also recruited through the Encephalitis Society for a study concerning children with a history of encephalitis. Their study recruited 36 participants from an initial sample of 89 families of children aged 10 – 17 years who were contacted through the Encephalitis Society database. This study achieved a 40% response rate.

With a maximum of 171 children on the Encephalitis Society database meeting the inclusion criteria for the current study it was considered that the necessary sample size could be achieved. Being the main national charity and support group for individuals post-encephalitis it was considered to be the most appropriate means of recruitment. In addition, with participants being required to complete outcome measures on one single occasion, it was felt unlikely that there would be significant dropout. Hooper et al. (2007), whose recruitment procedure was very similar to that proposed, experienced no drop out and did not report any problems with missing data.

Post hoc calculations

Thirty eight participants were recruited to this study, with 33 being included in the final sample due to missing data for five participants. This sample is lower than was anticipated, and was identified within the priori power calculation, and therefore careful consideration was given to carrying out statistical analyses on

this sample. As the time identified for recruitment had ended and all of the potential participants meeting the inclusion criteria on the Encephalitis Society database had been invited it was considered that further recruitment would not be possible. Priori power calculations had sought for medium correlation effect sizes of 0.3. A previous study published by Hooper et al. (2007) with a similar recruitment procedure through the Encephalitis Society reported correlation effect sizes of between .321 and .590. These indicate medium to large effect sizes with a similar sample size and methodology. Based on these effect sizes it was considered appropriate to continue with statistical analysis and post hoc power calculations were calculated.

Post hoc power calculations were carried out for primary and exploratory correlations and the multiple linear regression. For the primary correlational stage of this study a G*Power: Version 3.0.8 (Erdfelder, Faul & Bucher, 1996) calculation with a sample size of 33, $p < 0.05$ and effect sizes of -.74 and -.77, calculated power of 0.99 for both primary correlations. Power for each of the exploratory correlations identified power of 0.9 for the correlation between sleep difficulties and the PedsQL™ score. Power was found to be lower than 0.8 for the correlations between age at time of illness and diagnosis of epilepsy and indicates that further investigation of these variables in future research is warranted. Power of 0.9 was found for the multiple linear regression based on a G*Power: Version 3.0.8 (Erdfelder, Faul & Bucher, 1996) calculation with a sample size of 33, $p < 0.05$ and R^2 of .71.

These calculations indicate high levels of power for the primary correlations and multiple linear regression, though lower power for some of the exploratory correlations indicate that further variables of interest should be considered in future research.

1.10. The Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Measure

The Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Measure (Varni, Seid & Rode 1999) parent report version was chosen as the measure of parent/carer reported HRQL of children in this study due to its good psychometric properties and applicability across conditions. The PedsQL™ is a 23 item inventory asks parents/carers to identify how much of a problem their child/adolescent has had with certain items in the past month. Items include: physical functioning, such as walking 100 metres, running and having aches and pains; emotional functioning, such as feeling afraid or scared, feeling angry and feeling sad; social functioning, such as getting on with other children/teens, getting teased by other children/teens and keeping up with other children/teens; and school functioning, such as paying attention in class, keeping with schoolwork and missing school because of not feeling well. For each item parents/carer are asked to identify how often their child has had this problem: never; almost never; sometimes; often; or almost always.

Varni, Limbers and Burwinkle (2007) demonstrated the reliability and validity of the PedsQL™ generic core measure parent report version in a sample of 13,878 parents. They found that 2.1% of data was missing when the measures were completed by parents, concluding that this demonstrated the measure as feasible for parent/carer completion. This study demonstrated internal consistency reliability alpha coefficients exceeding the minimum 0.70 for group comparison and 0.90 for individual analysis, across parent-proxy report for children/adolescents within the 2 – 16 years age range. It also demonstrated construct validity through the known groups approach, demonstrating statistically significant differences between HRQL scores for healthy children and parent proxy-report for children with a known chronic health condition. The effect sizes of these analyses were found to be mostly within the medium (.50) to large (.80) effect size range.

A previous study by Varni, Seid and Kurtin (2001) also demonstrated internal consistency reliability for the total scale score (alpha = 0.90), the physical health summary score (alpha = 0.88) and the psychosocial health summary score (alpha = 0.86) for the parent report version of the PedsQL™ generic core measure. These studies have the advantage of large sample sizes and inclusion of both healthy and clinical populations. Varni et al. (2001) included samples of healthy, acutely ill and chronically ill children in their study. The psychometric properties of the PedsQL™ have been further highlighted in systematic reviews of QoL measures for children and adolescents where the

reliability, validity and sensitivity to change of the PedsQL™ measure were identified (Eiser & Morse, 2001b; Solans et al., 2008).

A number of alternative paediatric QoL measures are identified within the literature (Eiser & Morse, 2001b; Solans et al., 2008). Frequently reported measures include the Child Health Questionnaire (Landgraf, Abeltz & Ware, 1996), the KINDL-R Revised Children Quality of Life - Questionnaire (Ravens-Sieberer & Bullinger, 1998) and the Generic Health Questionnaire (Collier, 1997). A systematic review by Solans et al. (2008) highlighted that the PedsQL™ and Child Health Questionnaire both demonstrate good reliability, validity and sensitivity to change. Further to this, Ronen, Streiner, Rosenbaum and the Canadian Pediatric Epilepsy Network (2003) have highlighted that both measures are gaining recognition as child focused and broad based measures of health.

The practicalities and design of the current study were considered in choosing the most appropriate HRQL measure. The design of this study was a postal survey inviting parents/carers of children with potentially severe disability to take part. Therefore, a significant factor to consider was the length of time to complete measures. This was particularly important as parents/carers were being requested to complete multiple measures. The PedsQL™ has been identified to be quicker to complete than the Child Health Questionnaire with

Eiser and Morse (2001a) identifying the Child Health Questionnaire to be completed in 20 minutes and the PedsQL™ in only 5 – 10 minutes.

Consideration was also given to the use of a generic or disease-specific HRQL measure (see 1.6 for further discussion on generic versus disease-specific measures of HRQL). For the current study it was felt that a generic measure would be most applicable. Due to the rarity of encephalitis, a condition-specific measure for children post-encephalitis is not available in the literature. In addition, due to the heterogeneous nature of the consequences of encephalitis HRQL measures specific to traumatic brain injury and epilepsy may not capture the wide variation in neurological and psychological consequences and it therefore does not seem appropriate to consider it alongside any other specific condition. Also as this was an exploratory topic area where little prior research has been conducted it seemed most appropriate to consider HRQL in relation to the general population rather than to children with another condition that may not be meaningfully compared with children post-encephalitis.

The PedsQL™ has been found to have higher rates of agreement due to its objective nature (Upton, Lawford & Eiser, 2008). It has been indicated by a number of authors that rather than parent-proxy being an unreliable means of assessing HRQL of children it is simply another means of assessing it from a parents' perspective, although it is considered that, where possible, gaining a

measure of both the child's and parents' report is advantageous (Punjabi, 2008, Varni et al., 2007).

The use of the PedsQL™ in a postal survey was also considered. As the PedsQL™ parent report version is a self-administered measure that parents complete alone it was not considered to be a concern for a postal survey. Issues that could have created difficulties due to a postal survey were problems of missing data if a parent/carer was unsure of a question being asked or unsure how it related to their child. The PedsQL™ is a relatively straightforward measure to complete and it was considered that this should help to reduce the likelihood of any of these problems. Additionally a contact telephone number for the chief investigator and the Encephalitis Society was detailed on the information sheet should parents/carers have any queries regarding the measures and how to complete them.

Taking into account the above considerations, the parent-proxy version of the generic core PedsQL™ measure was felt to be the most applicable in order to explore HRQL for children post-encephalitis.

1.11. Children's Memory Questionnaire (CMQ) (Drysdale, Shores & Levick, 2004)

The Children's Memory Questionnaire (CMQ) (Drysdale, Shores & Levick, 2004) is an adaptation of the Everyday Memory Questionnaire (EMQ) (Sunderland, Harris & Baddeley, 1983; Sunderland, Harris & Greaves, 1984) that was developed by Drysdale et al. (2004) in order to assess the suitability of the EMQ with children. The rationale behind this was that a memory questionnaire for children may be useful as an easily implemented first stage in the detection of memory difficulties. This was identified as important given the implications of memory in learning.

The CMQ is compiled from two versions of the EMQ (Sunderland, Harris & Baddeley, 1983; Sunderland, Harris & Greaves, 1984). Wording of items was not changed substantially and consisted only of substituting verbs such as "forgets" for "forgetting". The CMQ consists of 30 of the 35 items of the original version of the EMQ (Sunderland, Harris & Baddeley, 1983) plus three new items from the revised 27-item version (Sunderland, Harris & Greaves 1984). Items that were taken out were those that were deemed unsuitable for children due to considerations regarding their developmental status. These included four items referring to reading and writing (items 14, 15, 16, 17 respectively of Sunderland, Harris & Baddeley, 1983) and another referring to absent-mindedness and doing things not intended (item 29 of Sunderland, Harris &

Baddeley, 1983). One item from Sunderland, Harris & Baddeley (1983) (Forgetting where you have put something and losing things around the house) was divided into two items.

The 34 item questionnaire asks parents/carers to identify how much of a problem their child/adolescent has with certain items. Examples of items include; forgets where she/he has put something, loses things, forgets what she/he was told a few minutes ago, starts to say something then forgets what it was she/he wanted to say and fails to recognise someone she/he met for the first time recently. For each item parents/carer are asked to identify how often their child has had this problem on a scale of one to seven: 1) never or almost never happens; 2) about once in 3 months; 3) about once a month; 4) about once in 1-2 weeks; 5) about once or twice a week; 6) about once a day; 7) more than once a day.

Drysdale et al. (2004) found the CMQ to have poor positive predictive power, but high negative predictive power. Its poor positive predictor power indicates that as a diagnostic tool it may be over-inclusive and incorrectly classify individuals who do not have a memory deficit as having one. The finding of high negative predictive power, however, suggests that it could be useful in confirming negative diagnosis of memory deficit. The current study is not concerned with identifying whether a child would or would not meet the criteria for a memory deficit but is seeking a general measure of how their parent/carer

reports their everyday memory difficulties. Therefore, for the purposes of this study the questionnaire provided an adequate means of acquiring a measure of parent/carer reported memory problems from a questionnaire that has been used with healthy and clinical child populations (Drysedale et al., 2004). Drysdale et al. (2004) do not detail in their study how the measure was presented to the parents, for example by post, by telephone or in person. As the measure is a self-administered questionnaire and parents/carers in the current study were provided with a telephone contact for the chief investigator and Encephalitis Society for any queries, it was felt reasonable to use this questionnaire in a postal survey.

Consideration was given to the use of alternative measures. At the time of this study being carried out, however, very few tests of everyday memory were evident in the literature. The Rivermead Behavioural Memory Test: Children's Version (RBMTC) (Wilson, Ivani-Chalian & Aldrich, 1991) was reported to be a standardised measure of everyday memory in children. However, this test was a face-to-face neuropsychological test to be carried out directly with children and was therefore not deemed to be conducive to a postal survey seeking parent/carer report.

The CMQ was therefore chosen for its utility in providing a parent-proxy assessment of their child's memory, its acceptable level of reliability and

conducive use to a postal survey. In addition it was easily completed for parents/carers who may have children with significant health needs.

1.12. Behaviour Rating Inventory of Executive Function (BRIEF)

The Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy & Kenworthy, 2000) is comprised of a Behavioural Regulation Index (BRI) score, a Metacognition Index (MI) score and an overall General Executive Composite (GEC) score. The BRI is identified as representing a child's ability to shift their cognitive set and modulate their emotions and behaviour through appropriate inhibitory control. The MI represents a child's ability to initiate, plan, organise and sustain future problem solving in their working memory. This index is seen as reflecting the ability of a child to cognitively self-manage tasks and reflects their ability to monitor their performance. The MI is related directly to a child's ability to actively problem solve across a number of different contexts.

The BRIEF is based on a definition of executive functions that is represented as an umbrella construct that includes a collection of interrelated functions that are responsible for purposeful, goal-directed, problem-solving behaviour. It has been found useful in evaluating executive function impairment in children with a range of developmental and acquired neurological conditions such as traumatic brain injury (Mangeot, Armstrong, Colvin, Yeates & Taylor, 2002), attention-

deficit-hyperactivity disorder (ADHD) (Jarratt, Riccio & Siekierski, 2005; Mares, McLuckie, Schwartz & Saini, 2007), hydrocephalus (Mahone, Zabel, Levey, Verda & Kinsman, 2002), autism (Gilotty, Kenworthy, Sirian, Black & Wagner, 2002) and epilepsy (Parrish et al., 2007).

The 86 item inventory asks parents/carers to identify how often their child/adolescent has had problems with certain items over the past six months. Items include; BRI items such as, gets out of control more than friends, becomes upset with new situations, blurts things out, small events trigger big reactions angry or tearful outbursts are intense but end suddenly and thinks too much about the same topic; MI items, such as feeling afraid or scared, feeling angry and feeling sad; social functioning such as, needs to be told to begin a task even when willing, has a short attention span, has trouble with chores or tasks that have more than one step and cannot find things in room or school desk. For each item parents/carers are asked to identify how often their child has had this problem: never; sometimes; or often.

There are a number of measures available that are aimed at assessing a child's executive function on the basis of a proxy-report, for example, the Child Behaviour Checklist (Achenbach, 1991) and the Conners Behaviour Rating Scale (Conners, 1989). The BRIEF differs from these measures in that it is the only standardised parent-report measure that was specifically designed to assess executive function. Other parent-report measures such as the Child

Behaviour Checklist are concerned with the overall behaviour of the child rather than particularly focussing on specific aspects of executive function. A further strength of the BRIEF is in its relationship with the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan & Kramer, 2001). In a study by Parrish et al. (2007) it was found that the BRIEF significantly correlated with the D-KEFS, demonstrating the utility of parent ratings in the assessment of executive function. This study also examined the Child Behaviour Checklist alongside the BRIEF and the D-KEFS and found that the BRIEF was a significantly stronger predictor of executive function impairment on the D-KEFS than was the Child Behaviour Checklist.

1.13. Demographic/illness specific questionnaire

This questionnaire was used to gain information regarding demographics in order to be able to describe the clinical population which had been investigated in this study. This included gathering information regarding the child's gender, age and age at time of their encephalitic illness. Whilst the age and gender of the child were used to describe the sample, age at onset was considered important given the literature on the impact of sustaining brain injury at a young age when full development of cognitive function and capacity has not yet occurred (Dowell et al., 2001; Rautonen, Koskiniemi & Vaheri, 1991; Starza-Smith, Talbot & Grant, 2007).

Further information regarding illness specific factors were asked of parents/carers with respect to their child. Parent/carers were asked what type of encephalitis their child had been diagnosed with. They were given a number of options as well as boxes indicating 'not sure' or 'unknown' cause. This question was considered necessary given research that has indicated specific patterns of brain damage and impairment specifically following HSE (Tunkel et al., 2008), as well as providing an indication of the prevalence of encephalitis types within this sample population. This is an important factor given research indicating that for a percentage of cases the cause of encephalitis remains unknown (Davison et al., 2003; Tunkel et al., 2008).

In addition, parents/carers were asked whether their child had been treated with the anti-viral medication, acyclovir, at the time of their encephalitis illness, and if so for how long they had received this treatment. This was considered important given literature detailing improvement in outcome for individuals treated with acyclovir (McGrath et al., 1997) and more specifically the findings of Elbers et al. (2007) who found that there was less prevalence of neurological consequences for children who were treated for 21 days or more, in comparison to those treated for 14 days.

Parents/carers were also asked to indicate whether their child had received a diagnosis of epilepsy since their encephalitic illness. The purpose of this question was that there is a substantial body of evidence and literature

regarding epilepsy and HRQL as summarised in section 1.6. As 50% of children post-encephalitis are reported to have epilepsy (Dowell et al., 2001) this was an important factor to consider and analyse with respect to HRQL of children post-encephalitis.

As discussed in section 1.7 when detailing and discussing the justification for the inclusion criteria of the study, participants were not excluded if they had any pre-morbid or co-existing developmental or medical conditions. The reason for this was that this could greatly limit recruitment of a heterogeneous clinical population who are likely to have a number of medical complaints. Rather than being excluded from the analysis, details of any pre-morbid or co-existing conditions were considered when analysing and interpreting the data for this population.

The final question that was asked of parents/carers on the demographic/illness specific questionnaire was whether their child had experienced sleep difficulties post-encephalitis. This question was imperative due to research that has indicated a significant relationship between sleep and QoL (Mitchell & Kelly, 2008), and the fact that sleep difficulties are highlighted as a potential problem for children post-encephalitis (Encephalitis Society, 2005). It was explained that this research would not be specifically focussing on sleep difficulties, however, it was necessary to gain this information in order to consider its relationship with

children's HRQL post-encephalitis and its potential influence as a confounding variable. See section 1.6 for further discussion of sleep and HRQL.

1.14. The Encephalitis Society and recruitment procedure

The Encephalitis Society is a United Kingdom based charity set up in 1994 by, and to support, those people affected by encephalitis. As well as providing support and information to people nationally and internationally, they contribute to raising awareness of the condition and encouraging ongoing research helping to further understand the causes and consequences of encephalitis. Their stated aim is to improve the QoL of all people affected directly and indirectly by encephalitis. The society holds a database of over 3,000 people who have been affected by encephalitis, including children and adults.

The use of a postal survey through the Encephalitis Society was deemed to be the most effective way in which to reach as many people on a national basis who met the inclusion criteria for this study.

1.15. Ethical considerations

Based on guidance from the British Psychological Society's (BPS) 'Ethical principles for conducting research with human participants' (2009) a number of ethical considerations were made during study design.

Parent/carer consent and child assent

Due to the children/adolescents in this study being between the ages of 8 and 15 years old it was felt that parental informed consent as well as child assent where possible should be employed. Careful consideration was made to the issue of child assent throughout the design of this study. It was important that as parents/carers would be providing information relating to their child, the children/adolescents assent for their parents/carers to participate should be considered. However, as some children were likely to have cognitive impairment some may have not been able to understand the information sheets and give their assent. It was felt important to have the child assent within the pack, whilst leaving it to the parent/carer's discretion as to whether they consent and complete the questionnaires. It was clearly stated in the information sheets to parents/carers that any questionnaires that were returned with a completed parent/carer consent form would be included in the study, whether or not a child assent form was included. It was not possible to know prior to sending out the packs which children had what degree of cognitive ability or impairment. Questionnaires that were returned without child assent, but with a signed and completed parent/carer consent form were included in the study.

The inclusion of parent consent and child assent was decided upon based on guidance from the BPS (2009), as well as the World Medical Association's Declaration of Helsinki (2008), which are the ethical principles for medical research involving human subjects.

The BPS's (2009) guidance states that, "research with children or with participants who have impairments that will limit understanding and/or communication such that they are unable to give their real consent requires special safe-guarding procedures" (point 3.2). They go on to state that:

"where possible, the real consent of children and of adults with impairments in understanding or communication should be obtained. In addition, where research involves any persons under 16 years of age, consent should be obtained from parents or from those in loco parentis. If the nature of the research precludes consent being obtained from parents or permission being obtained from teachers, before proceeding with the research, the investigator must obtain approval from an Ethics Committee" (BPS, 2009, point 3.3).

The World Medical Association Declaration of Helsinki (2008) indicates that "for a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative" (point 11). They go on to state that "when a potential research subject who is deemed incompetent

is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative” (point 12).

It is believed that these guidelines have been met as far as possible in this study design where children/adolescents have been given the opportunity to provide their assent. Of the 38 who responded all were returned with a completed parental consent form and 36 with a completed assent form. This could indicate a bias where more families who could gain assent from their children responded. It is not possible to ascertain how many families declined to take part due to a child not giving their assent.

Deception

The purposes of the study were made clear to participants in full, in order to ensure fully informed consent. Information sheets were provided that contained information regarding the purposes of the study and versions were specifically designed for parents/carers and for children. The child information sheets were adapted for each age group in order to account for developmental level. Parents/carers were asked to read through the information sheets with their children if their child was not able to do so independently. All information sheets were designed based on guidance from the NHS National Research Ethics Service (2008). See Appendix B, C and D for information sheets.

Debriefing

Parents/carers were informed through the information sheets at the time of recruitment that a summary of the study results would be made available to the Encephalitis Society once completed. Participants and their parents/carers were informed that they could gain access to the study results from the society. It was also highlighted that the results would be written up as a university doctoral thesis and with the aim of publication in an academic journal. It was made clear to parents/carers that individual feedback on their child/adolescent's results was not possible.

Withdrawal from the investigation

Participants and children/adolescents were informed of their right to withdraw from the study. Due to participants only being requested to respond on one occasion, it was explained that should they wish to not take part they were free to discard the recruitment pack with no affect to theirs or their child's care.

Protection of participants

In the information sheets sent to potential participants and their children, a contact number for the chief investigator was provided should they have any

questions or queries regarding the study. Participants and their children were also assured of confidentiality. Parents/carers were asked not to put any personal or identifiable information on the measures that were sent back to the investigator. The questionnaires were coded, and the list of participants and their codes kept separately from the questionnaires in a secure lockable filing cabinet at the University. It was not possible to ensure anonymity as the questionnaires were returned with the completed consent forms and if any parents/carers were requesting any specific help or support it was decided through the ethical process that it may be necessary to contact them through the Encephalitis Society. The information sheets included a section to reassure parents/carers that some difficulties are usual for any child/adolescent and that they should not worry if their child has some of the traits (e.g. all children have problems doing homework or experience low energy at times). It was suggested, however, that if they did need to talk to someone due to issues raised in the questionnaire they should contact the Encephalitis Society and a contact number for the society was made available.

In consideration of the demands and pressures already on parents/carers consideration was given to the length of time to complete the outcome measures. Each of the measures was predicted to take approximately 10 – 15 minutes to complete. Therefore, in total, the measures and demographic/illness specific questionnaire took an estimated 40 - 60 minutes to complete by the parent/carer, and they were able to do this at a time that suited them. There

were no costs incurred by participants, and their parents/carers, as the postage to return the questionnaires was covered by a research budget provided to the chief investigator by the University.

Issues regarding gaining ethical approval

A number of ethical alterations and decisions were made in response to considerations and comments made by the University and NHS ethics panels. Whilst the majority of these were minor amendments to the wording of the information sheets/consent forms or invitation letters, one query that was highlighted by the NHS ethics committee and seriously considered for the study was the issue of parental/carer informed consent and child/adolescent assent. The committee questioned whether child/adolescent assent was necessary and whether questionnaires returned without assent would be excluded. As identified earlier in this section this was considered in great depth and following further clarification on the justification of child assent and parental/carer consent, the ethics committee accepted their inclusion. The final decision was to include child assent in order to consider those children/adolescents who may wish to provide their assent to take part, but leave it to parents/carers to provide overall consent to be included in the study.

2. Extended results

2.1. Missing data

In the current study five questionnaire packs that were returned contained missing data. One pack did not include a completed PedsQL™, one did not include a completed PedsQL™ or demographic/illness-specific questionnaire, one did not include a completed PedsQL™ or BRIEF, one did not include a completed PedsQL™ or BRIEF and one did not include a completed BRIEF. Given the extent of missing data for each case it was felt most appropriate to exclude the five cases from the primary and exploratory analysis. This process was employed based on guidance from Field (2009) that case-wise deletion is recommended when conducting multiple regression.

On further investigation of the missing data, two of the parents/carers who had not completed measures, though had returned the packs, had indicated on their responses that they could not complete the measures due to the severity of their child's disability and felt that the measures did not capture the difficulties that their child faced. This could present a bias by which those parents/carers with children with greatest disability may not have responded. This should be considered when interpreting the data and could direct towards future research to look at alternative methodologies which may provide greater opportunity for

participation to those families with a child with more severe disability. Previous literature has highlighted the problems that can occur with non-response bias when utilising postal surveys (Edwards et al., 2002; MacDonald, Newburn-Cook, Schopfacher & Richter, 2009). Edwards et al. (2002) conducted a systematic review of randomised controlled trials (RCTs) that included any method for influencing response to postal questionnaires. This included 292 RCTs and 258,315 participants. This review highlighted strategies that were found to increase response to postal surveys, such as monetary incentives, short length of questionnaires, stamped addressed envelopes for returning measures, contact with potential participants prior to survey and research originating from universities. While these strategies have been identified as advantageous in increasing response rate, MacDonald et al. (2009) highlight that non-response bias is not necessarily corrected for by a large sample size. They identify the need to consider how well the sample can be generalised to the population from which it is looking to explore, due to the risk of non-respondents being those who may have responded differently to those who did respond.

(See extended discussion 3.4 for further discussion on response rate and sample size and 3.6 for recommendations for future research).

2.2. Distribution of data

Data was initially visually explored for normal distribution through the use of histograms and normality curves. In addition, calculations of z-skewness, z-kurtosis, Kolmogorov-Smirnov and Shapiro-Wilk were conducted in order to numerically explore whether the data was normally distributed.

Histograms and normality curves

Histograms with normality curves were produced for each continuous variable, including the variables of age, age at time of illness, physical health, psychosocial health and total health scores of the PedsQL™, CMQ total score, and the BRI, MI and GEC scores of the BRIEF (see Figures. 1 - 9).

Visual examination of the histograms suggests a clear positive skew in Figure 2. This histogram and curve indicates a skew whereby there is a larger proportion of participants reporting a younger age at time of illness. This is consistent with encephalitis prevalence rates reported in the literature which present increased prevalence of encephalitis in children and even greater prevalence in infants under the age of one (Health Protection Agency, 2005). Visual examination of Figures 8 and 9 indicate a negative skew. These histograms suggest that the sample presents a greater proportion of higher scores on the MI and GEC of the BRIEF. This is not a surprising outcome given

findings in the literature that executive function impairment is frequently reported following encephalitis in children (Dowell, et al., 2001; Hooper et al., 2007).

Figure 1. Histogram and normality curve for age of child participants

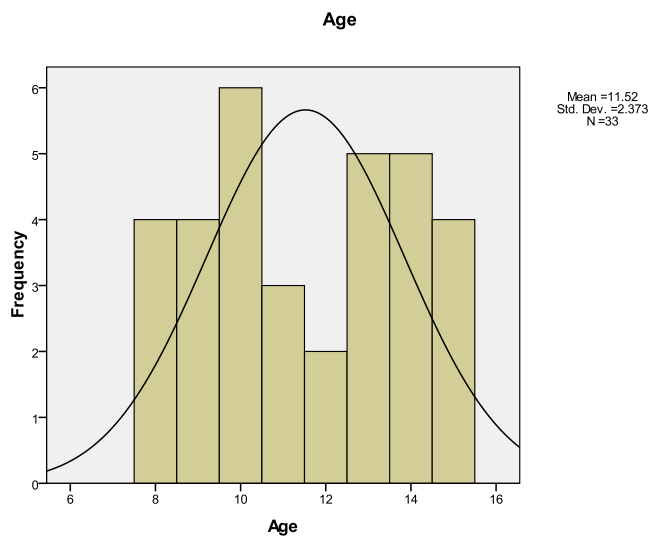


Figure 2. Histogram and normality curve for age at time of illness

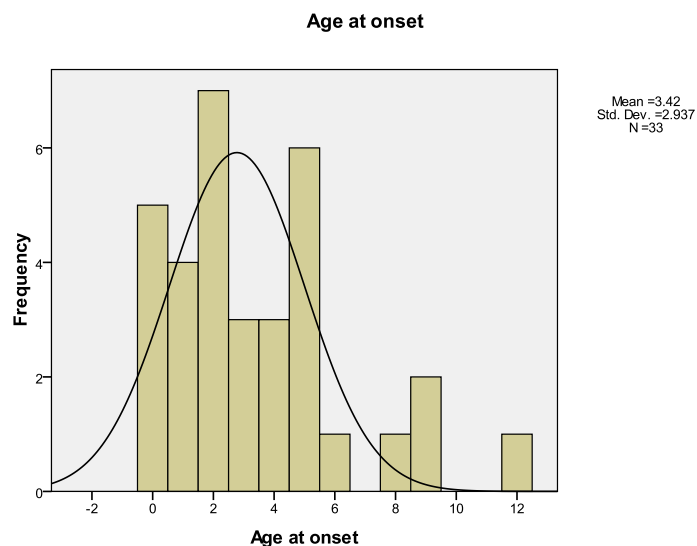


Figure 3. Histogram and normality curve for PedsQL™ Physical Health Score

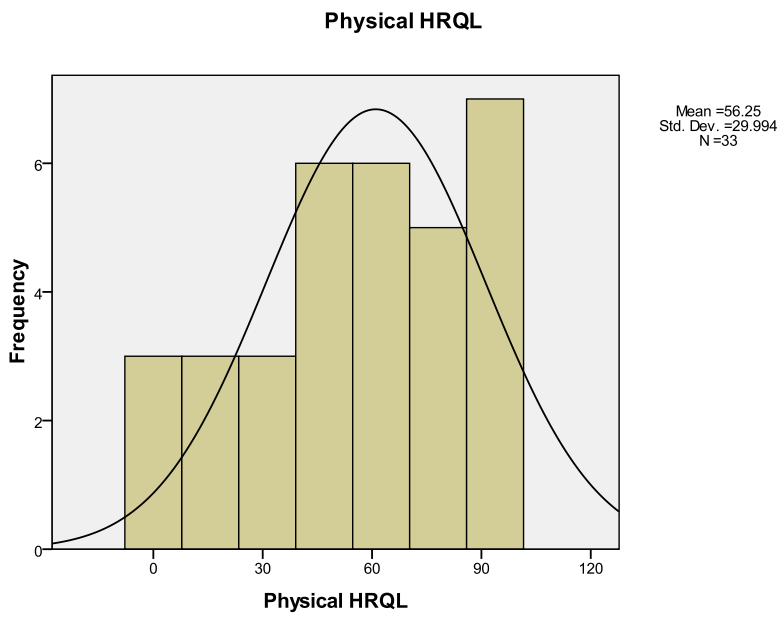


Figure 4. Histogram and normality curve for PedsQL™ Psychosocial Health Score

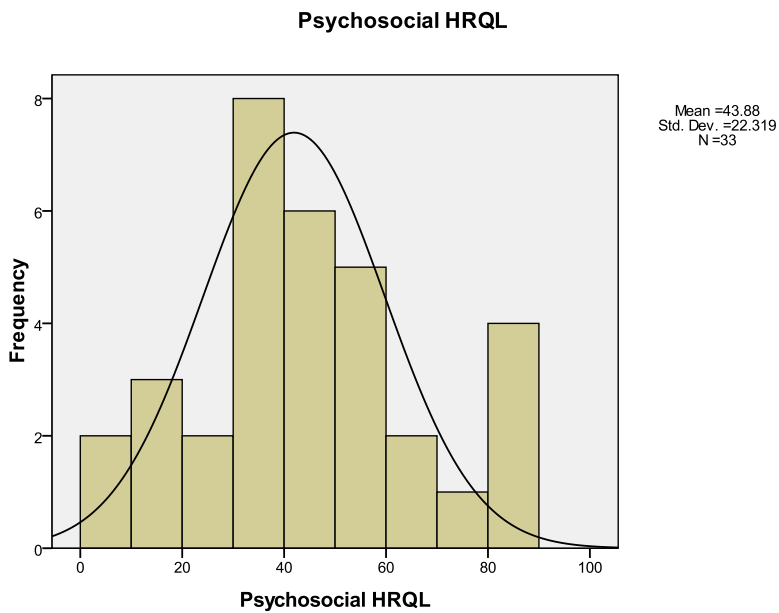


Figure 5. Histogram and normality curve for PedsQL™ Total Health Score

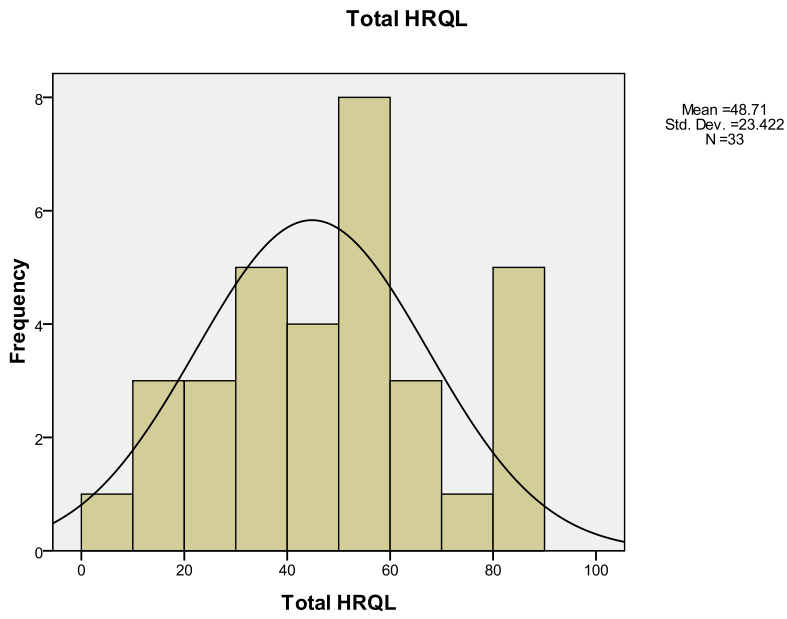


Figure 6. Histogram and normality curve for CMQ Total Score

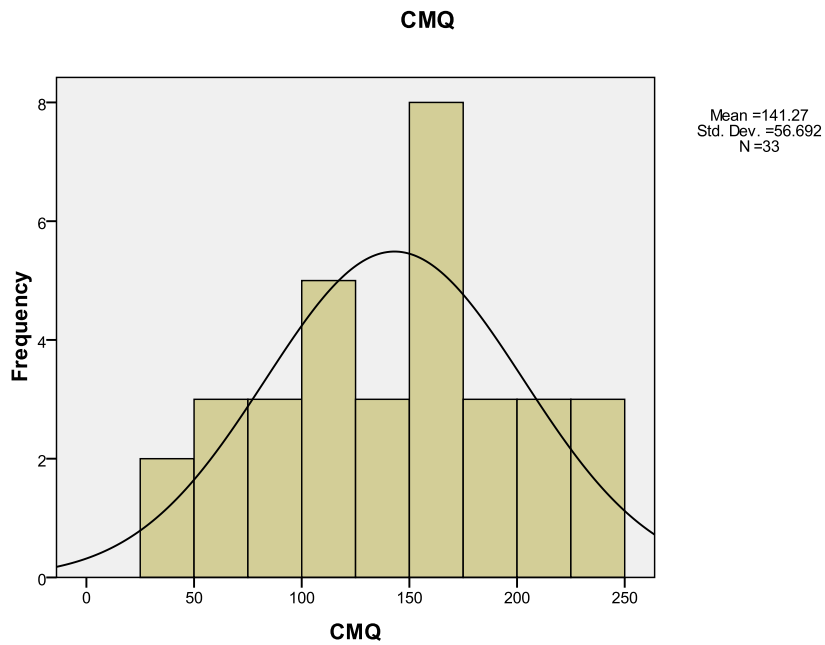


Figure 7. Histogram and normality curve for BRIEF BRI Score

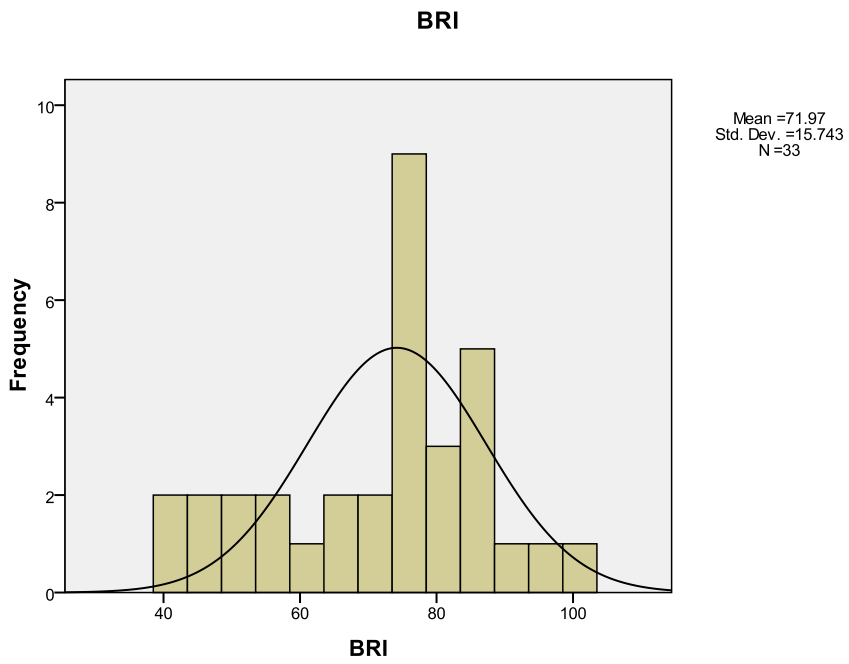


Figure 8. Histogram and normality curve for BRIEF MI Score

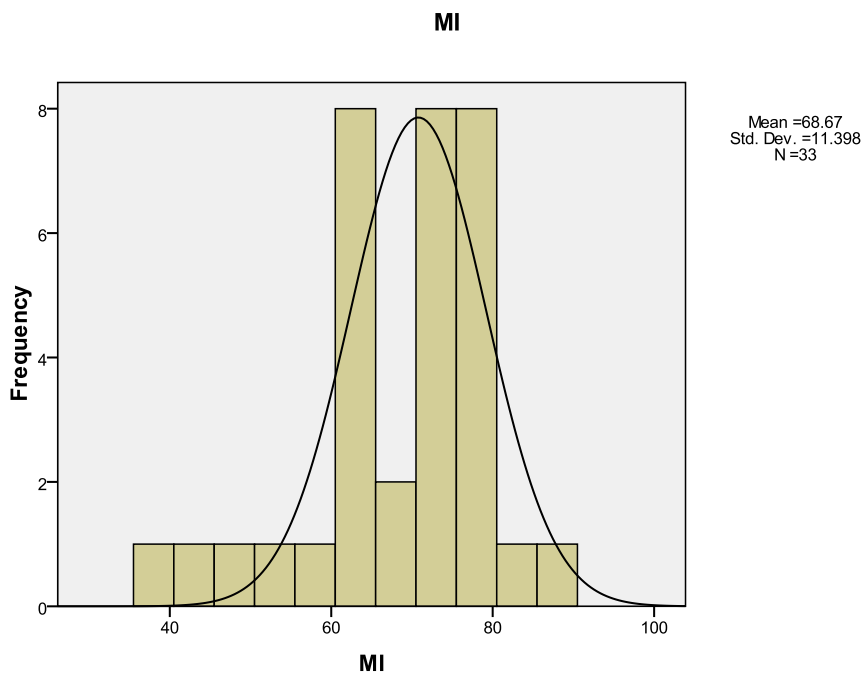
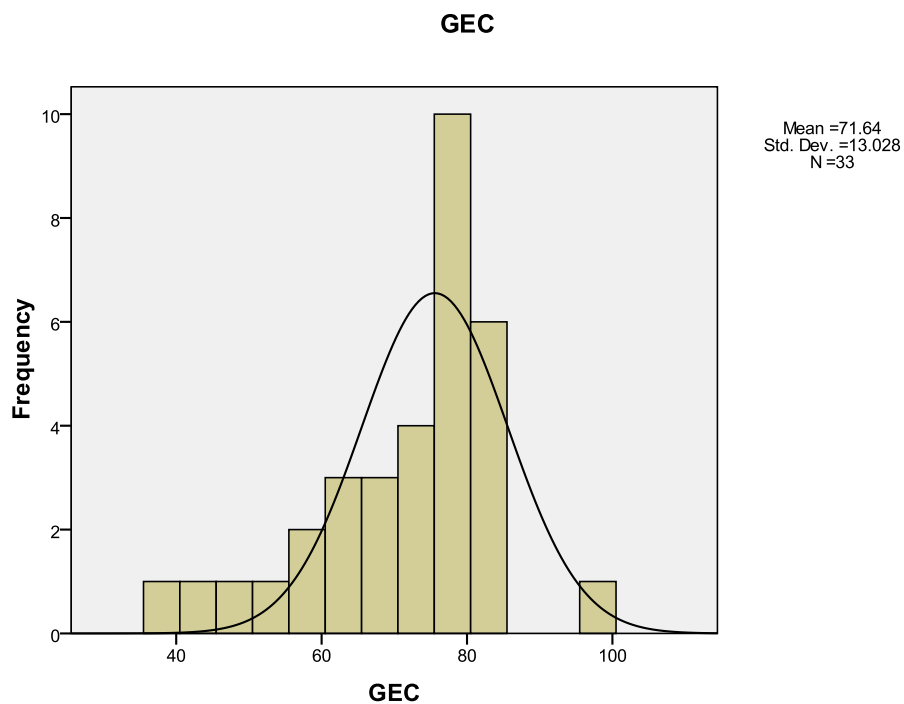


Figure 9. Histogram and normality curve for BRIEF GEC Score



For the variables of age, physical health score, psychosocial health score and total health score from the PedsQL™ and the BRI score from the BRIEF it was difficult to ascertain normal distribution visually and therefore further examination of normality was necessary.

Skewness and Kurtosis

Whilst histograms and normality curves allow an initial inspection of distribution, producing values of skewness and kurtosis allow further quantification of normality through numbers. Values of skewness and kurtosis should be found

to be zero in a normal distribution (Field 2009). This suggests that the further away the value is from zero the more likely it is that the data is not normally distributed. Positive skew values indicate that there are too many low scores in a distribution whilst negative skew values indicate too many high scores in a population. Table 5 details skewness and kurtosis values for each continuous variable. As is evident in the table, a number of variables produce skewness and kurtosis figures that deviate from zero.

Whilst skewness and kurtosis values are helpful, the assumptions are that the data set has a mean of zero and a standard deviation of 1 (Field, 2009). As the means and standard deviations differ greatly between the measures that are being used it is recommended that the scores of skewness and kurtosis are converted to z-scores (Field 2009). This enables all the data sets to be converted to having a mean of zero and a standard deviation of 1 to allow us to accurately consider their distribution and whether it deviates from the norm.

z-scores for skewness and kurtosis were calculated using the following equation and are presented in Table 5.

$$Z_{\text{skewness}} = \frac{S - 0}{SE_{\text{skewness}}} \quad Z_{\text{kurtosis}} = \frac{K - 0}{SE_{\text{kurtosis}}}$$

Significant values of z-skewness for age at time of illness, and for the MI and GEC scores of the BRIEF suggests non-normal distribution of these variables.

Table 5. Skewness, Kurtosis and z-skewness and z-kurtosis for all Continuous Variables

	Skewness (Std error = .409)	z-skewness	Kurtosis (Std error = .798)	z-kurtosis
Age	-.01	.02	-1.39	-1.74
Age at time of illness	1.10	2.69**	1.11	1.39
<i>PedsQL™</i>				
Physical Health Score	-.35	-.86	-1.03	-1.29
Psychosocial Health Score	.33	.81	-.27	-.34
Total Health Score	-.04	-.10	-.64	-.80
CMQ Total Score	-.12	-.30	-.83	-1.04
<i>BRIEF</i>				
BRI	-.46	-1.12	-.59	-.74
MI	-.95	-2.32*	.72	.90
GEC	-.88	-2.15*	.59	.74

Note: * $p < .05$ ** $p < .01$

Kolmogorov-Smirnov and Shapiro-Wilk

Kolmogorov-Smirnov and Shapiro-Wilk tests allow further examination of the distribution of data. These tests compare the scores in the sample to a normally distributed set of scores with the same mean and standard deviation (Field, 2009).

Table 6. Kolmogorov-Smirnov and Shapiro-Wilk Distribution Statistics for all Continuous Variables

	Kolmogorov-Smirnov		Shapiro-Wilk	
	Statistic	Sig.	Statistic	Sig.
Age	.16	.03*	.91	.01*
Age at time of illness	.17	.02*	.90	.00**
<i>PedsQL™</i>				
Physical Health Score	.10	.20	.94	.07
Psychosocial Health Score	.15	.06	.96	.23
Total Health Score	.07	.20	.97	.58
CMQ Total Score	.11	.20	.97	.40
<i>BRIEF</i>				
BRI	.18	.01**	.95	.13
MI	.19	.00**	.92	.02*
GEC	.18	.01**	.92	.02*

* $p < 0.05$ ** $p < 0.01$

Values of Kolmogorov-Smirnov and Shapiro-Wilk for this study are presented in Table 6. Significant Kolmogorov-Smirnov values for age, age at time of illness, and both index scores and the composite score of the BRIEF, as well as significant Shapiro-Wilk values for age, age at time of illness and the MI and GEC scores of the BRIEF, indicate that the variables of age, age at time of illness and the index and the composite scores of the BRIEF are not normally distributed.

2.3. Use of the Bonferroni correction

A Bonferroni correction, or adjustment for multiple tests, is when a more stringent criterion is applied to test for statistical significance than the conventional $p < 0.05$. A Bonferroni correction is used when a researcher is conducting multiple tests on a sample of data and is calculated as the original alpha level ($p < 0.05$) divided by the number of comparisons being made. The reason for applying this comparison is to reduce the chances of making a type I error. A type I error is made when the null hypothesis is rejected when it was in fact true (a false positive).

Much debate is had regarding the use of Bonferroni correction, or other multiple comparison adjustments, in the analysis of statistical data. Textbooks on statistics in psychology recommend their use in order to reduce the chances of type I error (Dancey & Reidy, 2007; Field, 2009). Implications that have been

identified of using a Bonferroni correction, however, are that whilst reducing the likelihood of making a type I error, it reduces statistical power and increases the chance of making a type II error (Nakagawa, 2004; Perneger, 1998). A type II error is made when a null hypothesis fails to be rejected when it is false (a false negative).

Perneger (1998) wrote in an article titled 'What's wrong with Bonferroni adjustments', in the British Medical Journal, that Bonferroni corrections should not be applied when assessing evidence about specific hypotheses due to the increased risks of making type II errors and reducing statistical power. Perneger (1998) suggests that simply documenting explicitly what has been done and why, should enable the reader to reach a reasonable conclusion without using the Bonferroni adjustment. Nakagawa (2004) supports this argument, and recommends the reporting of effect sizes as an alternative.

For the current study, a number of multiple comparisons were made. Consideration was given to the use of a Bonferroni correction or alternative multiple comparison adjustment.

On consideration of the literature it was decided a Bonferroni correction should be applied to the analyses of this study in order to account for the number of multiple comparisons particularly given the limited sample size. The number of comparisons analysed in this study was 21, therefore the alpha level of 0.05

was divided by 21 in order to give rise to an alpha level of 0.002. As recommended by Perneger (1998) as well as adjustment through use of a Bonferroni correction, this study has explicitly presented the statistical analyses that were conducted in order to allow the reader the opportunity to interpret the results themselves and reach their own conclusions.

2.4. Demographic/illness specific information

Collection of demographic and illness specific information was collected from parents/carers regarding their child. This provided a picture of the clinical sample that was recruited which enabled comparison with the general clinical population of children post-encephalitis, as well as consideration of the presence of any confounding variables.

Demographics

Demographic information demonstrated that 45.5% of the children in the sample were male. This demonstrates a relatively even ratio of males and females and is consistent with gender ratios seen in previous research looking at paediatric samples post-encephalitis (Hooper et al., 2007; Koskiniemi et al., 1997). The age of the children recruited for this study was spread through a range of eight to 15 years and therefore covers the range of ages that were being specifically investigated in this sample. Exploring the range more closely

51.5% of the sample was between the ages of eight and 11 years, and 48.5% between the ages of 12 and 15 years. This provides an even spread of children/adolescents across the age range of investigation. The ethnicity of children/adolescents was not evenly spread with 87.9% being classified as white British. This may indicate a bias whereby individuals and families from more diverse ethnic groups are not accessing support through the Encephalitis Society or alternatively this may reflect encephalitis as being more prevalent in this ethnic group. The Health Protection Agency is currently conducting an epidemiological study regarding encephalitis and this may provide further exploration and clarification on this finding. As identified in the journal paper, age at time of illness presented a mean of 3.42 (SD = 2.94), with 49% of the sample having a history of encephalitis before the age of three years. This is consistent with prevalence rates that demonstrate higher incidence in young children (Health Protection Agency, 2005).

Illness specific information

Information collected from parents/carers regarding their child's encephalitic illness revealed that 54.5% of children were diagnosed with infectious encephalitis, such as herpes simplex virus encephalitis. Twenty seven percent were identified by their parents/carers as having had post acute encephalitis, such as acute disseminated encephalomyelitis (ADEM) and one was identified as having another type of encephalitis that they did not specify. This spread of

aetiology is not unusual given the literature which indicates that infectious encephalitis is more prevalent in the population (Stone & Hawkins, 2007). In this study sample, 9.1% of parents/carers identified that their child's encephalitic illness had been of unknown origin and two parent/carers was unsure of the type of encephalitis. This is much lower than percentages of cases identified in previous studies and literature (Davison et al., 2003; Granerod & Crowcroft, 2007; Hooper et al., 2007). For example, Hooper et al. (2007) found 27% of their sample was diagnosed with encephalitis of no identified origin.

Parents/carers were also asked about their child's treatment, specifically focusing on whether their child had received the anti-viral treatment acyclovir and if so for how long. With research indicating differences in outcome dependent on length of time of acyclovir treatment this was considered to be an important factor to consider (Elbers et al., 2007; McGrath et al., 1997). It was identified that 75.8% of the sample were reported to have received the treatment acyclovir at the time of their encephalitic illness. This finding is not surprising given guidance that recommends the initiation of acyclovir treatment in all cases of suspected encephalitis (Tunkel et al., 2008). Only 12.1% of participants had not received acyclovir and 12.1% of parents/carers reported that they were unsure whether their child had received the treatment or not. With regards to length of time of treatment, 45.5% of parents/carers reported that they were unsure of how long their child had received acyclovir. Twenty

four per cent indicated that their child had received the treatment for less than 14 days, 6% for 14 – 20 days and 12.1% for 21 days or over. The remaining 12.1% of the sample did not answer this question as they had not received the treatment. These figures provide an insight into parent/carers knowledge of their child's treatment. Whilst the majority of parents/carers could identify whether their child had received acyclovir, 45.5% were not sure of the length of time that their child received this. Due to the sample size and the numbers of participants within each group it was not considered appropriate to conduct additional statistical analysis on data regarding the type of encephalitis and treatment due to the numbers of parents/carers indicating that they were unsure of details.

The results of the illness specific questionnaire further indicated that 48.5% of children had been diagnosed with epilepsy since their encephalitic illness. This finding is consistent with the literature which has indicated figures of approximately 50% of children experiencing epilepsy post-encephalitis (Dowell; et al., 2001). Of the sample, 63.6% of parents/carers reported that their child had experienced sleep difficulties following their illness. Whilst further information regarding specific details of epilepsy and sleep problems was not collected in this study this helped to indicate the potential impact of difficulties in these areas.

Parents/carers were asked to detail any pre-morbid conditions that their child

had before their encephalitis illness. It was found that 21.2% of children had experienced some pre-morbid health condition. This constituted seven children. Developmental delay or possible developmental delay was reported for three cases (9.1%). Problems in pregnancy (3%), dyslexia (3%), asthma (3%), cerebral palsy (3%), and possible hearing problems (3%) were also identified as pre-morbid concerns. Three cases of developmental delay in this sample pre-illness indicate 9.1% of the sample. With prevalence of developmental delay in the general child population being up to as much as 10% (Hartley, Salt, Dorling & Gringras, 2002) this suggests that pre-illness the sample does not deviate significantly from findings in the general population.

Parents/carers were also asked to detail any chronic medical conditions/concerns that were apparent following their child's illness. Due to the heterogeneity of outcome following encephalitis it was important to consider the impact of possible confounding variables and therefore this information was collected to consider any additional medical/health concerns that children were experiencing post-illness. It was reported that 66.7% of the sample experienced some chronic health concern post-illness. The health concerns are identified below with figures for the percentage of participants in the whole sample experiencing these concerns;

- Visual (18.2%) and hearing (3%) impairments
- Epilepsy (48.5%)

- Hemiplegia (12.1%)
- Headaches/Migraine (6%)
- Autistic Spectrum Disorders (9.1%)
- Speech and language problems (9.1%)
- Incontinence (3%)
- Anxiety and obsessive-compulsive disorder (3%)
- Behavioural problems (6%)

This information suggests that children are experiencing a range of health concerns following their encephalitic illness. Collection of this information was important as it demonstrates the health problems and concerns that may be apparent for children/adolescents post-encephalitis. Collection of this information helps to identify some of the difficulties that children may face following encephalitis. However, it should also be considered that this was an open question to parents/carers and while examples were provided regarding the types of concerns they may have, such as visual or hearing impairment and epilepsy, parents/carers may have interpreted the question differently or had a different view on what they considered to be a particular health concern. The influence of these health concerns as potential confounding variables should also be considered. For the most part, only one or two children/adolescents were reported to experience a particular health concern, however, a higher percentage of children were reported to experience epilepsy (48.5%), visual

impairments (18.2%) and hemiplegia (12.1%). Due to the constraints of this study further detail, and more structured questioning, regarding health concerns was not possible, though future research may consider exploring this in greater detail, utilising more specific and sensitive measures that are not so open to subjective interpretation.

2.5. Further correlational analysis of subscale scores

Hypothesis 1

In addition to the primary analyses, the GEC was found to be significantly negatively correlated with the psychosocial health score ($r_s(33) = -.86, p < .001$) and the physical health score ($r_s(33) = -.63, p < .001$). The MI was significantly negatively correlated with the total health score ($r_s(33) = -.71, p < .001$), the psychosocial health score ($r_s(33) = -.77, p < .001$) and the physical health score ($r_s(33) = -.60, p < .001$) of the PedsQL™. The BRI was significantly negatively correlated with the total health score ($r_s(33) = -.57, p < .001$) and the psychosocial health score ($r_s(33) = -.72, p < .001$) of the PedsQL™. The BRI was not the correlated significantly with the physical health score ($r_s(33) = -.47, p < .01$) of the PedsQL™.

Hypothesis 2

The CMQ score was found to significantly negatively correlate with the psychosocial health score ($r(33) = -.76, p < .001$) and physical health score ($r(33) = -.71, p < .001$) of the PedsQL™.

2.6. Exploratory correlational analysis of subscale scores

Further correlational analysis was carried out between the variables of age at onset of illness, diagnosis of epilepsy, presence of sleep difficulties, and the subscale scores of the PedsQL™.

Non-parametric spearman rho correlations were conducted with the variable of age at onset of illness due to the sample being not normally distributed (see 2.2. for discussion on distribution of data). Age at onset did not correlate significantly with the physical health score ($r_s(33) = -.11, ns$) or the psychosocial health score ($r_s(33) = -.05, ns$) of the PedsQL™.

Point-biserial correlations were conducted with the variables of diagnosis of epilepsy and presence of sleep difficulties due to these being dichotomous variables with a yes or no response. Presence of sleep difficulties was found to significantly correlate with the psychosocial health score ($r_{pb}(33) = .60, p <$

.001), but not with the physical health score ($r_{pb} (33) = .37, ns$) of the PedsQL™. However, diagnosis of epilepsy did not correlate significantly with either the physical health score ($r_{pb} (33) = .18, ns$) or the psychosocial health score ($r_{pb} (33) = .38, p < .05$) of the PedsQL™.

2.7. Assumptions met for conducting a multiple regression

In order to test the assumptions for conducting a multiple regression, guidance from Dancey and Reidy (2007) was followed. The following assumptions were explored prior to, and during, analysis to ensure that each assumption was met and the regression model could be accurately interpreted.

Make sure you have enough participants

This study reached a sample size of 33 for final data analysis. On the basis of Stevens (1986) this is sufficient for conducting a multiple linear regression with three predictor variables. Stevens (1986) suggests that valid results for regression can be achieved with a sample size of 10 participants per predictor variable. With a sample size of 33 there were 11 participants per predictor variable for this multiple linear regression.

The criterion variable should be drawn from a normally distributed population of scores

Dancey & Reidy (2007) indicate that in order to carry out a multiple linear regression the criterion or outcome variable must be from a normally distributed population of scores. They suggest, however, that the predictor variables do not need to meet this assumption. In this study the criterion variable of the PedsQL™ total health score is from a normally distributed population of scores (see 2.2. for distribution of data) and therefore meets this assumption.

Variables should be linearly related to the criterion variable

In a multiple regression, the predictor variables should be linearly related to the criterion or outcome variable (Dancey & Reidy, 2007). Scatterplots produced to look at the relationship between CMQ scores and total health score of the PedsQL™ and the GEC score of the BRIEF and the PedsQL™ total health score support the finding that these variables are linearly transformed and therefore meet the criteria for use in a multiple linear regression (see Figures 10 and 11 for scatterplots). These linear relationships have been supported in the significant negative correlations that have been found between them. The variable of sleep difficulties is a dichotomous variable that demonstrates a significant correlation with the PedsQL™ total health score.

Figure 10. Scatterplot and line of best fit of PedsQL™ total health scores and CMQ scores

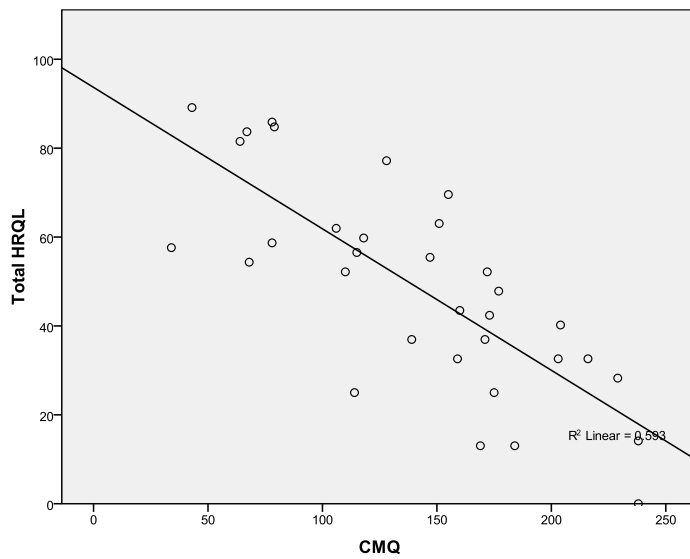
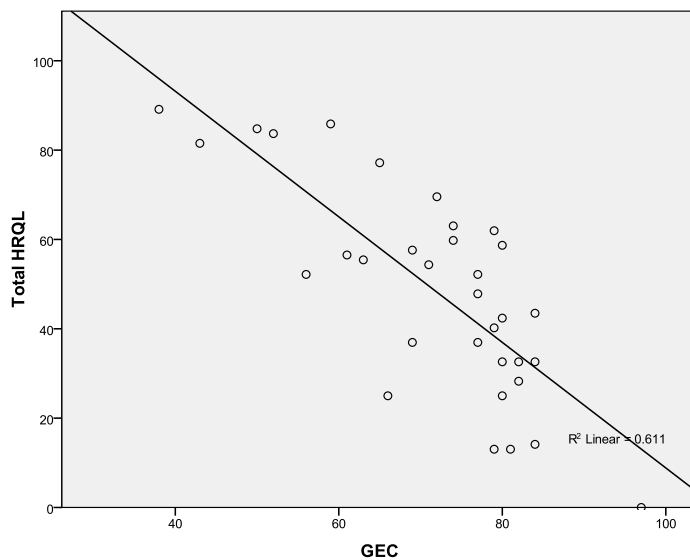


Figure 11. Scatterplot and line of best fit of PedsQL™ total health scores and GEC scores of the BRIEF



The variables included in the regression meet the criteria of inclusion as Field (2009) highlights that multiple regression should involve quantitative variables that are either continuous or categorical (with two levels).

Outliers may need to be eliminated

Dancey & Reidy (2007) highlight the need to consider whether any extreme outliers are present in the data and if so whether they should they be removed. Field (2009) provides guidance on observing the presence and impact of outliers in multiple regressions.

Field (2009) considers exploring residuals, which allows exploration of differences between the values of the outcome predicted by the regression model and the actual values of the outcome observed in the sample. Any residuals that are present then reflect the error that is present in the regression model. These unstandardised residuals, however, are reported to be difficult to interpret in regression models as they are measured in the same units as the outcome variable and it is recommended that z-scores, or the standardised residuals, allow better guidance (Field, 2009). On investigation of the multiple regression carried out in this study, one standardised residual was highlighted in the output which required greater inspection. The standardised residual for case 31 was at a value of -2.20. Field (2009) provides guidance on what are accepted values of residuals. Field (2009) suggests that if more than 5% of

cases have standardised residuals above a value of 1.96 then there is evidence that the model is a poor representation of the data. He also identifies further criteria that no more than 1% of cases should be greater than 2.58. In this study there is one case with a standardised residual above 1.96 but below 2.58. This converts to 3% of cases in this model having a value greater than 1.96 and therefore suggests that the model is an acceptable representation of the actual data.

Multicollinearity

The final assumption that Dancey and Reidy (2007) recommend for a multiple regression is to ensure that there is no multicollinearity within the model. Multicollinearity is when there is a strong correlation between two or more predictor variables within a regression model (Field, 2009). Field (2009) presents literature that suggest that a variance inflation factor (VIF) of more than 10 (Myers, 1990) should indicate that multicollinearity may be biasing the model. In this study the VIF scores were found to be 1.40 for the variable of sleep difficulties, 2.34 for the CMQ score and 2.85 for the GEC score. It is also suggested that a tolerance statistic of below 0.2 is cause for concern (Menard, 1995). In this study the tolerance levels for the predictor variables were 0.72 for the variable of sleep difficulties, 0.43 for the CMQ score and 0.35 for the GEC score. All three variables are above the threshold of 0.2 and are therefore not considered to be of concern.

Investigation of the regression model in this study suggests that multicollinearity is not a cause for concern and it therefore meets the assumptions for interpreting the multiple linear regression.

3. Extended discussion

3.1 Everyday memory, executive function and HRQL

As reviewed in the literature, memory difficulties and executive function impairment are found to be a frequently reported consequence of encephalitis in children. For children, memory difficulties and executive function impairments can be of significant concern due to their implications for learning and educational progress (Hooper et al., 2007; Kneen & Solomon, 2007), where memory, attention, concentration, planning and motivation is imperative for the acquisition and retention of new knowledge. This study has demonstrated that parents/carers do report problems for their children with memory and executive function following encephalitis which is consistent with previous literature (Benedict et al., 1998; Benjamin et al., 2007; Dowell et al., 2001; McGrath et al., 1997; Wood et al., 1989).

The findings of a significant negative correlation between these neuropsychological consequences and a child's parent/carer reported HRQL suggest that these difficulties may be impacting greatly on their lives and the lives of the family. When considering these findings further it was identified that parent/carer reported executive function and everyday memory were significantly correlated with both the psychosocial and physical summary scores of HRQL. The psychosocial summary score is comprised of emotional, social

and school functioning and may be an indicator of the importance of executive functioning and everyday memory for many areas of a child's functioning. Executive functioning following brain injury in children has been identified as potentially impacting on working memory, inhibition, shifting attention, planning, metacognition, decision making, discourse processing, social cognition and behavioural self-regulation (Levin & Hanten, 2005). These aspects of functioning are fundamental skills in a child's integration into the school and social environment. Emotional control could be seen to impact on a child's social integration with peers and adults, where motivation in a learning environment is of great importance, particularly as children grow up and are expected to become more independent in their learning and education as they progress through secondary education. Planning, organisation, concentration and attention also become increasingly important as a child travels through education, particularly as they enter secondary education and have a number of changes, such as classroom, subject and peer group, throughout the school day and year.

This study demonstrated further that parent/carer reported everyday memory and executive function were found to be significant predictors of parent/carer-reported HRQL. Although everyday memory was found to be the better predictor, the difference between the two variables was small. Determining causality in a correlational design is not possible, however this finding could be

speculated to be due to everyday memory and executive function having an impact on a large number of domains, including social and educational.

It is important to consider these findings alongside research which has found that executive function impairment correlates with high levels of parental distress (Hooper et al., 2007). The finding of a relationship between parental reported executive functioning and parental stress has been further highlighted in research in childhood ADHD (Joyner, Silver & Stavinoha, 2009). This research explored parental stress as measured by the Parenting Stress Index and parent reported executive function of their child, as measured by the BRIEF and the Children's Executive Functions Scale (CEFS). They found a significant correlation between parent's report of executive function and parental stress. These findings are an important consideration, as although the BRIEF has been found to demonstrate good reliability and validity as a measure of executive functioning in children, parent/carer completion in this study may have been influenced by other factors such as stress that they are experiencing.

This should also be considered when looking at the results of parent/carer reported HRQL of their child as research has indicated that parent/carer report can be influenced by the parent's attitudes, levels of stress or general health and well-being at the time of completion. For example, Kirpalani et al. (2000) found that parental hope significantly correlated with their reports of the HRQL

of their child with spina bifida. It is important to consider the potential influence of these factors when interpreting the results of this study.

3.2. Exploratory findings

As is highlighted in the journal paper, consistent with findings in other clinical populations, parent/carer reported sleep difficulties were found to correlate significantly with parent/carer reported HRQL for this sample of children following encephalitis. However, these analyses also demonstrated that age at onset of illness and diagnosis of epilepsy did not correlate significantly with parent/carer reported HRQL. This is inconsistent with findings in the literature (Rautonen, Koskiniemi & Vaheri, 1991; Ronen, Streiner & Rosenbaum, 2003).

Age at time of illness

There was no relationship found between age at onset of illness and parent/carer reported HRQL. This was considered to be an important area of investigation as prior research has indicated that age at onset of encephalitis has an impact on outcome, such as degree of neurological impairment or specific difficulties (Dowell et al., 2001; Rautonen, Koskiniemi & Vaheri, 1991). Rautonen et al. (1991) reported a significantly higher risk of severe neurological impairment or death for infants under the age of one, which is five times greater than the risk in older children.

The finding of no significant correlation between age at onset of illness and parent/carer reported HRQL could be considered to be for a number of reasons. Whilst research has indicated poorer outcome in younger children following encephalitis (Rautonen et al., 1991) this finding has not always been replicated in further studies (Klein et al., 1994; Kolski et al., 1998). The specific location of brain damage caused by the encephalitic illness or plasticity of the developing brain, rather than primarily the age at onset of encephalitic illness, should be considered as potentially confounding variables.

Diagnosis of epilepsy

Inconsistent with the literature (Ronen, Streiner & Rosenbaum, 2003; Sherman et al., 2006) this study did not find a significant correlation between diagnosis of epilepsy and parent/carer reported HRQL. The findings did, however, partially support Sherman et al. (2006) who found that an increase in executive dysfunction in children with epilepsy led to a poorer HRQL.

Possible explanations for the differences found between this study and previous literature is that these findings may be specific to the clinical population of children following encephalitis. Alternatively, it is important to consider that information regarding the particular type of epilepsy or treatment for the child was not collected. It was therefore not identified whether the child's epilepsy

was mild, moderate or severe or whether seizures were well-controlled. This could be predicted to have an impact on a parent/carer's perception of their child's HRQL and it is therefore not known how representative this sample is from other clinical populations of children with epilepsy.

Presence of sleep difficulties

Sleep difficulties have been found to have a significant impact on HRQL of children (Mitchell & Kelly, 2008). The current study supports these findings in a sample of children following encephalitis. Sleep problems are identified to be a potential problem for children following encephalitis (Encephalitis Society, 2005) and this is demonstrated in the study sample, with over half of parents/carers reporting the presence of sleep difficulties. Whilst consistent with previous findings it is important to consider that this study was not investigating sleep difficulties in detail and simply asked parents/carers whether their child/adolescent had experienced sleep difficulties or not since their illness. Sleep problems could be seen to be on a continuum and without guidance, or more specific questioning, parents/carers may have been using different metrics with which to answer this question. On the demographic/illness specific questionnaires that were sent to parents/carers it was explained that the study would not be able to consider the details of sleep problems in more detail due to the constraints of the research, though if significant relationships were found further research may be recommended. Therefore, the finding of a significant

relationship warrants further investigation of this topic area. While time and resource constraints were a concern in this study, future research in the topic area could consider the use of more specific questions such as how many hours sleep does your child get, do they sleep through the night or how many times do they wake in the night on average. Whilst this would not be a definitive measure it may provide further detail without over burdening potential participants.

3.3. Clinical implications

This study has highlighted significant relationships between parent/carer reported neuropsychological impairments and parent/carer reported HRQL. In considering the clinical implications of these findings, it has been highlighted that neuropsychological rehabilitation in order to aid children's recovery and develop strategies for reducing or managing these difficulties is very important. A recent study exploring children's QoL from the parent's perspective following childhood TBI is that carried out by Limond, Dorris & McMillan (2009). Results indicated that one to five years post-TBI 40% of parents reported their child's QoL to be reduced. This finding has also been supported by McCarthy et al. (2006). Limond et al. (2009) conclude in their paper that there is need for acute-follow up and rehabilitation for children and their families following brain injury. The findings of this study and those in other areas of acquired brain injury have to be considered within the context of rehabilitation provision.

Previous literature has highlighted the limited rehabilitation services for children post-acquired brain injury (ABI) in the United Kingdom (UK) (Starza-Smith et al., 2007). Many of the services in the UK have been found to be charity led or privately managed and in most cases rehabilitation is found to be conducted through recommendation to parents and teachers of strategies to use at home and school (Walker & Wicks, 2005). An example of one of the few centres of excellence for rehabilitation following ABI is the Children's Trust, a national charity based in Tadworth, Surrey. This centre provides tailored residential and outreach services to children with multiple disabilities, including those with acquired brain injury, within an interdisciplinary team of professionals and therapists including doctors, nurses, occupational therapists, physiotherapists, speech and language therapists and psychologists. With services such as these limited in the UK the importance of neuropsychological assessment and support to families and teachers in aiding a child's rehabilitation and recovery is highlighted. Research has demonstrated that late childhood and adolescence is a time of significant development of the frontal cortex of the brain and executive function development (Blakemore & Choudhury, 2006). As frontal brain injury and impairment in executive function skills are frequently observed in children post-encephalitis, identification of impairments at an early stage may help to prepare parents/carers, families and professionals, for the potential difficulties for their child, particularly during adolescence and puberty, when executive function impairments may become more apparent.

This study also demonstrated a significant relationship between sleep and parent/carer reported HRQL in children post-encephalitis. It is acknowledged that children following encephalitis may experience problems with sleep (Encephalitis Society, 2005) and it is important that these difficulties are identified and children/adolescents and their families are helped to manage these difficulties to ensure this does not impact adversely on their lives. It is not known how many children/adolescents who experience sleep difficulties in this population receive help and support with these problems, though the findings would indicate that it is an important area of need for some children/adolescents and should not be overlooked. Sleep problems, leading to possible tiredness and fatigue during the day, could significantly impact on a child's social and educational functioning.

As well as highlighting the specific neuropsychological rehabilitation and sleep needs of children post-encephalitis, the needs of parents/carers and the rest of the family are also considered. A number of parent/carer recruitment packs were returned where parents had entered further detail than was requested regarding their child's encephalitic illness. This could suggest that parents/carers are eager to share their journey regarding their child's encephalitic illness, possibly as a reflection of their wanting to help with research in the topic area. Suggestions for further qualitative research would allow parents to provide their own insight into their child's illness which could

greatly benefit the evidence base regarding childhood encephalitis and the impact on children and their families. Importantly, parent/carers eagerness to tell their story may also reflect the need for greater therapeutic support for families to talk through and share their stories.

3.4. Limitations of the study

Response rate and sample size

The current study received a response rate of 22%. This consists of 38 parents/carers agreeing to take part in the study from a total of 171 who were invited to take part. Whilst this enabled investigation of an under-researched topic area, the small sample made it difficult to explore the data in great depth because of concerns regarding multiple comparisons and manipulation of the data. In addition to the small sample size, of those parents/carers who did respond a proportion were unsure of some of the answers to questions, for example, being unsure of their child's encephalitis diagnosis or unsure of their child's treatment or length of time of treatment. In some ways this could be seen as informative as it may indicate the lack of information provided to parents/carers by medical staff involved in their care or alternatively the trauma of their child experiencing such a potentially fatal condition. The lack of certainty regarding these issues therefore created difficulties in exploring these with

regards to HRQL as the numbers of children in each category were too small to explore using inferential statistics.

The small sample therefore raises concerns about how representative it is of the clinical population from which it came. On comparison of the demographic and illness-specific information of this sample with previous literature and epidemiology studies, the data appears to be generally comparable (see extended results 2.4. for further discussion of demographic and illness specific information). MacDonald et al. (2009) have highlighted the importance of considering non-response bias in research utilising postal survey, indicating that a large sample does not necessarily account for this. This study looked to increase recruitment by invitation through a national charity recruiting over a wide geographical area, and using parent/carer report to allow participation for those children with all levels of cognitive ability. While the response rate for this study may appear relatively low, the sample does appear to be generally comparable with the clinical population from which it was recruited and power of at least 0.9 has been found for the primary correlations and multiple linear regression calculated in this study. (See extended discussion 3.6 for further discussion on recommendations for future research and increased sample sizes).

Practicalities of research

A number of financial considerations were made throughout this study. As a doctoral thesis has a limited research budget, there was some restriction to the quantity of recruitment that could be conducted. Despite careful planning and costing, this research had a relatively expensive recruitment procedure, as recruitment packs were sent out on the off chance that they would be returned. Additional costs, that were not budgeted for prior to recruitment, were also incurred via recruitment through the Encephalitis Society. This included additional costs for coding the questionnaires as requested through ethical consideration of the study. In order to reduce cost as much as possible, the chief investigator carried out most of the preparation of the recruitment packs prior to sending for posting out by the Encephalitis Society. Whilst this study has proved to be relatively costly, it was felt that this was the most advantageous recruitment procedure in order to recruit as widely as possible across a relatively rare population of children/adolescents following encephalitis.

An alternative recruitment procedure could have been to send an initial invitation to parents/carers and ask them to opt in before sending out the full recruitment pack with outcome measures. Whilst this may have limited the costing of a number of the outcome measures, it would have also increased postage through two further sets of postage, one to send out the invitations and

another for parents/carers to send back their acceptance. This method would also involve parents/carers being required to respond on two occasions, once to the invitation and secondly to the recruitment pack. This would increase demands on parents/carers who may already be under a great deal of pressure from caring for a child post-encephalitis. A further consideration would have been to request parents/carers to send back any uncompleted questionnaire packs in order that outcome measures that were not completed could be recycled for future research or clinical use.

Outcome measures

The outcome measures employed in this research were chosen based on a review of those available in the literature, the reliability and validity of each measure and the appropriateness of their use in the methodology of this study (see extended background 1.10, 1.11, 1.12 and 1.13 for further discussion of measures). Following exploration and statistical analysis of the data from this study, some considerations have been given to the use of certain measures in this research.

The CMQ was chosen as a measure of everyday memory as perceived by the parent/carer. This allowed for correlation with parent/carer reported HRQL to consider the hypothesis being tested. Since the study was carried out, a new measure has been introduced in the literature which could improve the

measurement of everyday memory in children as observed by the parent/carer. The Observer Memory Questionnaire – Parent Form (OMQ-PF) (Gonzalez et al., 2008) is identified as requiring further development, though in initial stages of development it has been identified as demonstrating internal consistency and significant correlation with a learning task. This measure should, therefore, be considered for any future research investigating parent/carer reported everyday memory in children.

The demographic/illness specific questionnaire included questions asking the parent/carer whether their child had experienced sleep difficulties since their encephalitic illness. Whilst the study provided some consideration of sleep and found a significant relationship between the presence of sleep difficulties and parent/carer reported HRQL, the measure of sleep difficulties was a simple yes or no answer which did not allow further exploration of specific sleep difficulties and the extent of these. Any future research in the area of sleep and HRQL in children post-encephalitis should use more specific and sensitive measures of sleep.

Additional information

This study aimed to gain as much information as possible regarding the participants and their encephalitic illness. On reflection there is information that may have been advantageous to have included in the demographic/illness

specific questionnaire. Certain information regarding the parent/carer respondent was not requested in this study. This results in not knowing whether the respondent was a mother, father, grandparent or other relative or carer of the child. Whilst this information was not imperative to investigating the set hypotheses, it may have provided an insight into whether there are any differences between parent/carer dependent on their relationship to the child. This information has been collected in previous research into this clinical population (e.g. Hooper et al., 2007). Whilst this may be of interest, this study was focussing specifically on the child participant, whereas Hooper et al. (2007) were specifically exploring parent/carer distress and coping.

Further information regarding the child's illness was not accessible to the investigator due to conducting a postal survey through a charity. This resulted in missing data for some participants where parents/carers were unsure or did not have knowledge of specific aspects of their child's illness, such as details about their child's treatment. Due to issues of confidentiality, and recruitment on a national scale, through postal survey, verification of any missing information was not possible. Further research in this area may find methodologies that allow access to medical information to verify such information an advantage. This would allow for more accuracy and improve information such as diagnosis and treatment. The missing data in this study can, however, be seen to provide some insight into the lack of information that parents/carers may have regarding details of their child's treatment and care, which could reflect a lack of

information being provided to parents/carers by medical professionals at the time of their child's illness. Alternatively this lack of detail could be due to the distress and trauma that parents/carers experience at the time of their child's illness which could impact on their ability to process and retain this information, particularly if increasing demands are placed on them as a consequence of their child's encephalitic illness.

3.5. Strengths of the study

The main strengths of this study are having opened up the topic area of encephalitis in childhood and parent/carer reported HRQL, and having provided recommendations of areas to consider for future research. Rather than simply exploring parent/carer reported HRQL it has focussed on those neuropsychological factors that are most frequently reported for children post-encephalitis in order to consider their relationship with parent/carer reported HRQL. There is evidence of specific patterns of impairment and brain damage post-encephalitis (Tunkel et al., 2008) and this study has helped to consider whether these specific patterns of impairment may relate to a person's HRQL following encephalitic illness in childhood. It differs from previous research as it focuses on the specific illness of encephalitis in children and particularly the neurological or developmental sequelae of acquired brain injury following encephalitis, such as epilepsy, specific neuropsychological impairment and sleep problems that are reported by children and their families. The outcomes

of the research result in a number of recommendations for future research. Childhood encephalitis is still an under-researched topic area and this study has helped to focus possibilities of future research in the area of HRQL, and more widely on the impact of childhood encephalitis on the child and those around them.

The methodology employed in this study allowed for recruitment on a national scale. This created greater opportunity for gaining the most representative sample of this clinical population as possible. The use of parent-proxy report aided this process. Parent-proxy in this context has allowed the possibility of gaining a more representative sample by not excluding those children who may have been unable to self-report due to cognitive impairment and/or communication difficulties.

A further strength of this research is its exploration of a real-life situation. The design has allowed for investigation of real individuals and their families and the impact of encephalitis on their lives. This ensures ecological validity as the methods, materials and setting of the study are a reflection of the real-life situation that is under investigation.

3.6. Recommendations for future research

Larger sample size

Future quantitative research in this topic area would benefit from greater sample sizes in order to increase power and generate more opportunities for multiple comparisons. The current study allowed for exploratory investigation between a number of variables specific to encephalitic illness in children and parent/carer reported HRQL. A larger sample would provide opportunity to consider further variables of interest such as type of encephalitis or length and time of treatment. Everyday memory, executive function and sleep difficulties were found to account for up to 71% of the variance of parent/carer reported HRQL and further exploration of variables may help to consider predictors that contribute to the remaining variance.

Edwards et al. (2002) have identified a number of strategies for increasing participation when utilising postal surveys in research, including strategies that consider incentives, length and appearance of questionnaires, delivery methods, and origin of research. This study attempted to follow these suggestions, as far as finances would allow, through consideration of measures based on length and time to complete, the use of stamped addressed envelopes for parents/carers to return measures, the use of colour on questionnaires to improve appeal and detailing sponsorship of the research

from the University of Lincoln. Whilst this was aimed to improve recruitment, future research in this topic area that is utilising postal survey, may look at further suggestions that have been found to increase response, such as monetary incentives, pre-warning communication of the upcoming research or reminders following recruitment packs being sent out. Whilst these strategies may increase costs they could improve response rates and should therefore be considered in any future research using postal survey. Though as MacDonald et al. (2009) identify, generalisability of the sample should still be examined to consider the impact of non-response bias irrespective, of the size of the sample.

Children's self-report of HRQL

Whilst moderate to high concordance rates have been found between child self-report and parent-proxy report of HRQL in some prior research (Majenemer et al., 2008; Theunissen et al., 1998; Verrips et al., 2000), there is also evidence that demonstrates low concordance (Cremeens et al., 2006; White-Koning et al., 2005; White-Koning et al., 2007). This study utilised parent/carer report and was therefore concerned with exploring a parent/carer perspective of their child's HRQL. In a clinical population where a proportion of children will experience significant cognitive impairment, parent/carer report was also necessary as it was not possible to know the cognitive ability of each child prior to invitation. This has opened up the area of HRQL in this clinical population,

however, this topic area would now benefit from exploration of self-reported HRQL of children post-encephalitis. This would permit consideration of concordance rates between self and parent-proxy report in this population and understand HRQL from the child's own perspective. The caution of this research would be that this may limit those children with severe disability and communication difficulties from participating and being able to present their self-report. This should be carefully considered in any future research in this area and wherever possible research should be made accessible to those with communication and cognitive difficulties.

Development of encephalitis specific HRQL measure

The generation and development of this study's design highlighted that a disease-specific measure of HRQL for encephalitis has not been found in the literature. This has been further highlighted by Wilson, Starza-Smith and Talbot (2008) who identify that the diversity that is apparent in the presentation of children post-encephalitis poses a challenge for neuropsychological rehabilitation. They highlight literature in which QoL is seen as one of the most desirable outcomes of post-encephalitis rehabilitation (Easton, Atkin & Hare, 2007). However, having looked at clinical cases they consider that the PedsQL™ may not fully encapsulate the unique QoL issues that are associated with the sequelae of encephalitis.

This study has highlighted that parent/carer reported HRQL is reduced in this study's sample of children post-encephalitis. Further research to consider the appropriateness of existing generic or disease-specific HRQL measures, such as the PedsQL™, may be warranted in order to establish whether the development of an encephalitis specific measure would be of clinical importance and value.

Age and executive function

Having highlighted research suggesting that development of executive function continues throughout childhood, adolescence and early adulthood (Blakemore & Choudhury, 2006), exploration of the impact of age on the relationship between reported HRQL and executive function impairment may be of interest. Further research exploring executive function impairments, age and HRQL could help to identify the impact of executive function impairment on children/adolescents at different ages and consider the impact of age-related development of the brain. Research in this area taking into account parent/carer report as well as self-report from the child/adolescent would allow further exploration of this topic area.

Qualitative methodology

This topic area would benefit from research of qualitative methodology.

Quantitative methodologies are advantageous in attempting to gain large sample sizes, allowing generation of information across wide variations in condition and quantifying specific cognitive impairments in a standardised way. This can help to explore difficulties in an objective way and compare them with healthy children or children with other chronic health or neurological conditions. From a number of the responses in this study it is clear that parents/carers were keen to tell their story. On some of the demographic/illness specific questionnaires that were returned parents/carers deviated from simply answering the questions and wrote additional comments on the sheet detailing more specific information regarding their child and the difficulties and circumstances around their illness. This reflects the emotional impact on parents/carers of this illness and their wish to tell more about their story and their child's journey through the illness and recovery. Specific research that explores parents/carers views of the impact of their child's illness on their child, as well as the children's own views of the impact of their illness on their life may add to the knowledge base of this condition. Again, this may limit accessibility to those children who are developmentally or cognitively able to participate themselves, though research of this sort would help to contribute to developing a greater understanding of factors related to encephalitic illness in childhood. Although standardised assessments allow quantification of HRQL that allows comparison across conditions and healthy samples, qualitative methodology would help to complement this information and provide a greater insight into specific factors that are identified freely by children and their parents/carers.

Collaborative research

Of great importance in the consideration of any future research in this topic area are the demands being placed on potential participants. Due to encephalitis being a relatively rare condition there is a risk that the same group of participants will be targeted for a number of different research studies. It is therefore important to consider collaboration with other researchers, in medical, psychological or other domains, to explore the possibility of sending out research invitations at the same time to reduce the number of times that potential participants are contacted. This could also incorporate more detailed collaboration with others in order to look at exploring areas of interest within the same piece of collaborative research.

3.7. Critical reflection on research and philosophy of science

All research can be seen at a fundamental level to develop from the general human desire to understand and make sense of the world around us (Dzurec & Abraham, 1993). Despite this general consensus, there is a traditional distinction observed between the quantitative and qualitative methodologies that are utilised within research (McEvoy & Richards, 2006). This study adopted a quantitative methodology. The quantitative imperative is the view that studying something scientific means measuring it (Michell, 2003). Correlational

studies have been identified as falling under the traditional, quantitative imperative in psychological research (Keeley, Shemberg and Zaynor, 1988).

It is often considered that quantitative methodologies, which use standardised measures and statistical analysis, originate from a positivist philosophical position (McEvoy & Richards, 2006). Positivism is a philosophical position in science in which the goal of knowledge is to describe the phenomena we experience. It considers the need to put aside any preconceptions in order to identify objective based on empirical observations (McEvoy & Richards, 2006). Essentially positivism holds the view that science is focused on what we can observe and measure. The goal of positivism is to identify generalisable laws based on the identification of statistical relationships between variables (Ackroyd, 2004). There is, however, much debate regarding positivism and quantitative methodologies. It has been argued by some, that positivism does not in fact dismiss the possibility of non-quantitative methods in psychology and therefore quantitative methods cannot be traced back solely to positivism (Michell, 2003). For example, it is highlighted that Carnap (1966), a logical positivist, indicated that not all sciences would find quantitative method useful and advocated that it should be up to the researcher to decide upon the tools that would be of most use. Michell (2003) discusses the view that it is not simply positivism from which the quantitative imperative can be traced, but from the Pythagorean doctrine, that viewed the natural world as being fundamentally

quantitative in structure. Miller (1999) also argues that quantitative approaches are not necessarily positivistic in any meaningful sense.

Alternatively, qualitative methodologies are interpretive approaches to research and enquiry, which are based on non-numerical narratives (McEvoy & Richards, 2006). These interpretive, qualitative, approaches are seen to place a greater emphasis on the way in which the world is socially constructed and understood (Blaikie, 2000). Methods of research include utilising tools such as focus groups, unstructured interviews and textual analysis (McEvoy & Richards, 2006).

Whilst taking a quantitative methodology in this research, it has been a process that has not ignored or been critical of qualitative approaches. There has been a gradual increase in the amount of qualitative research in clinical psychology. Its increase in use was highlighted in the late 1980's, by Keeley et al. (1988), who conducted a study in which they reviewed all clinical psychology dissertations undertaken over the previous twenty years. They found a small increase over the years in those projects taking a qualitative stance. This has been further reinforced by those such as Rennie, Watson and Monteiro (2002) who conducted a review of the literature and found a dramatic increase in qualitative research through the 1990's. They did, however, identify that much of the increase was due to the introduction of new journals specific to qualitative

methodologies rather than qualitative research being accepted by existing traditionally quantitative journals.

The reason for taking a quantitative approach in this study was due to the identified need to answer specific clinical questions, which were concerned with asking, whether factors and consequences of encephalitis in childhood are related to parent/carer reported HRQL. This study has relied on quantitative methodology as a means of clearly identifying these questions and exploring this in a more objective and measured way. In addition it has also used these findings to identify areas that may benefit from further quantitative, experimental research, as well as recommending qualitative methodologies in order to explore specific topic areas and questions that would lend well to qualitative research.

As highlighted in the literature by Carnap (1966), this study's methodology was utilised in order to find the most appropriate framework with which to answer the questions of concern. There are a number of ethical considerations that were important in the decision behind taking a quantitative stance. This was particularly influenced by consideration of informed consent and participation of children with a potentially wide range of cognitive and communication abilities. Due to the nature of encephalitis it has been highlighted that a proportion of children within the sample may have had significant communication difficulties due to their acquired brain injury. Consideration was therefore given to the most

appropriate means in which to gain a view of HRQL for this clinical population, while also trying to maximise recruitment in this under-researched topic area. The use of quantitative methodology was deemed most appropriate in order to explore this topic area by recruiting nationally through a charity and using parent-proxy measures to explore children of all cognitive abilities.

This study has enabled a critique of a solely quantitative stance and helped to consider the use of specific methodologies, quantitative and qualitative, dependent on the context and question to be answered. This was particularly highlighted when considering the richness of information that may be provided by parents/carers regarding their journey through their child's illness as indicated by extended answers to questions on the demographic/illness specific questionnaires for some parents/carers.

It is hoped that this research study has contributed to both providing new knowledge in an area of science in which little previous work has been conducted, as well as opening up new avenues and questions for gaining further new knowledge regarding encephalitis in childhood and HRQL. It is hoped that this will help in the aim of improving care for these children, in medical, psychological and neuropsychological domains, as well as help professionals and families in educational and home environments. This study has helped to aid confirmation of findings in previous research and literature, as well as highlight some differences. It is considered that these differences may

require further exploration in order to determine whether they are related to the specific and unique experiences of children post-encephalitis.

(Total thesis word count = 27, 108)

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Appendix A

Parent/carer invitation letter (Version 2: 29th January 2009)

(Letter printed on Encephalitis Society headed paper)

Dear Parent / Carer

As part of the Encephalitis Society's aims to promote research into encephalitis, we are supporting a study being carried out by Emily Talbot, a Trainee Clinical Psychologist, from the University of Lincoln. Emily is investigating the health-related quality of life of children and adolescents following encephalitis. Encephalitis in childhood is an area that requires further research and this study's aim is to open up this topic area to specifically consider what factors associated with encephalitis in childhood impact on a child/adolescents health-related quality of life.

I am sending the enclosed pack to people that I have identified from our database as parents/carers of a child or adolescent, currently aged 8 - 15 years old, who has contracted encephalitis at any time during childhood. If you feel that in your circumstances this is inappropriate or incorrect, I am very sorry, please let me know. If you would like to discuss any aspect of the study please contact me.

Enclosed is an information sheet for you and a second information sheet for your child. The information sheets further detail the study and what it would involve for you and your child if you agree to take part. Also enclosed are a consent form for yourself and an assent form for your child, as well as the questionnaires for the study and a stamped addressed envelope. If your child is unable to read or understand the information you are able to consent on their behalf. However wherever possible your child's understanding of the research and his/her assent to take part should be sought.

Please take time to read the information sheets before you and your child decide whether to take part. There are contact details on the information sheet should you have any further questions or concerns regarding the study.

Many thanks for taking the time to read this letter.

Yours Sincerely

Resource Centre Manager

Tel

Email

Appendix B

(Version 2: 29th January 2009)

(Letter printed on Encephalitis Society headed paper)

PARENT/CARER INFORMATION SHEET

Title of study: Health-related quality of life (HRQL) in children and adolescents with encephalitis

I am a Trainee Clinical Psychologist at the University of Lincoln and I would like to invite you and your child to take part in a research study. Before you decide whether to take part please read the following information carefully and where possible ask your child to read the child/adolescent information sheet also enclosed. I have included my contact details at the end should you like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Contracting encephalitis as a child or adolescent can have an enormous impact on a child/adolescent's life, as well as their family and friends. Two of the most commonly reported neuropsychological difficulties are everyday memory problems and executive function difficulties, such as difficulties in planning and organisation and controlling feelings and behaviour. This study aims to

investigate whether there is a relationship between these difficulties and other encephalitis specific factors, and health-related quality of life (HRQL) for children and adolescents after encephalitis.

Why are my child and I being invited?

As a parent/carer of a child or adolescent, currently aged 8 - 15 years old, who has contracted encephalitis at any time during childhood we are asking you and other parents/carers like yourself to help us in trying to investigate the impact of encephalitis on a young person's HRQL.

Do we have to take part?

It is up to you and your child to decide if you want to take part. After reading this information sheet, we will ask you and, where possible, your child to sign a form to show you have agreed to take part. You and your child are free to withdraw at any time, without giving a reason. This will not affect the standard of care your child receives. If you choose not to take part you can discard this pack with no consequences.

What will my child and I have to do?

If you are in agreement with taking part in the study you will be asked to complete the four short questionnaires enclosed. Where possible your child will be asked to read the information sheet enclosed and sign an assent form to

indicate that they are happy for you to take part; however they will not be required to do anything else.

Only you as a parent/carer will be asked to complete the questionnaires. The first is a questionnaire asking you some questions about your child and their encephalitic illness. There are three further questionnaires, asking you questions about your child. Each questionnaire should take approximately 10-15 minutes to complete, in total all four should take approximately 40-60 minutes and you are able to do this at home at a time that suits you. I would then ask that you to return the questionnaires together with your signed consent form and your child's assent form in the stamped addressed envelope (SAE) provided. To ensure confidentiality, please do not put any personal or identifiable information for you or your child on the completed questionnaires. Consent forms and questionnaires will be coded to ensure confidentiality and stored separately in a secure lockable filing cabinet.

What are the benefits of taking part?

We cannot promise the study will help you or your child individually but the information we get will help in increasing our knowledge of the impact of encephalitis on children/adolescents and help to inform treatment and rehabilitation and improve services available to children/adolescents and their families.

Will taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you and your child will be handled in confidence. All information which is collected will be kept strictly confidential, and any information about your child which leaves the hospital will have any identifiable details removed so that they cannot be recognised. The questionnaires that you complete will be coded and stored separately from your consent forms in order to ensure confidentiality. The data will be stored securely at the University of Lincoln for seven years, after which time it will be destroyed.

What will happen to the results of the research study?

The results of this study will be written up as a university doctoral thesis and it is anticipated that it will also be published in an academic journal. A summary of the results will also be provided to the Encephalitis Society, in the UK, allowing you access to the results yourself. Confidentiality will be maintained throughout this process, with you and your child not being identified in any report/publication.

How is the study being funding and monitored?

The University of Lincoln will be sponsoring the study and covering costs of postage for returning your questionnaires. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed

and given favourable opinion by an NHS Research Ethics Committee and the University of Lincoln Psychology Ethics Committee

What if I have any further questions or concerns about the study?

If you have a concern or query about any aspect of this study, please contact me and I will do my best to answer your questions (contact number). If you would like any independent advice about participating in research such as this study please contact the local NHS Research & Development office (contact no). Some difficulties are usual for any child/adolescent and you should not worry if your child has some of the traits (e.g. all children have problems doing homework or experience low energy at times), however, if you need to talk to someone due to issues raised in the questionnaire I would direct you to the Encephalitis Society in the UK, a charity aimed at supporting individuals and families after encephalitis and raising awareness through research (contact number).

Thank you for taking time to read this information sheet. If you and your child are happy to take part please sign the consent form, ask your child to sign the child assent form, and send back with the completed questionnaires in the SAE provided.

Emily Talbot

Address

Trainee Clinical Psychologist

Appendix C

(Version 2: 29th January 2009)

(Letter printed on Encephalitis Society headed paper)

CHILD INFORMATION SHEET (8-10 YEARS)

Title of study: Health-related quality of life (HRQL) in children and adolescents with encephalitis

We are asking if you would take part in a research project. Before you decide if you want to join in it is important to understand why the research is being done and what you will be asked to do.

What is research? Why is this project being done?

Research is a way we try to find out the answers to questions. We want to find out whether having encephalitis when you are a child affects your quality of life.

Why have I been asked to take part?

You have been invited to join our study because you have had encephalitis and you can help us to understand more about whether having encephalitis when you are a child affects your quality of life.

Did anyone else check the study is OK to do?

Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. This project has been checked by an NHS Research Ethics Committee and the University of Lincoln Psychology Ethics Committee.

Do I have to take part?

No. It is up to you. If you do, I will ask you to sign a form saying that you are happy to take part. Your parent/carer has also read an information sheet and will be asked if they are happy for you to take part.

What will I be asked to do?

All that you will have to do is sign a form, if you are happy to take part in the study. I will be asking your parents/carers to fill in some questionnaires about you and when you had encephalitis, for example, how old you were and what treatment you had. I will then ask your parent/carer to send the questionnaires back to me in the post. You will not be asked to complete any questionnaires yourself.

Will joining in help me?

We cannot promise the study will help you individually but the information we get might help treat and support young people with encephalitis in the future.

Will anyone else know I am taking part?

We will keep the information that your parent/carer gives us confidential. This means we will only tell those who have a need to know. We will only send out information that has your name and address removed.

What if I don't want to do the research anymore?

If at any time you don't want to do the research anymore, just tell your parents.

They will not be cross with you.

Appendix D

(Version 2: 29th January 2009)

(Letter printed on Encephalitis Society headed paper)

CHILD/ADOLESCENT INFORMATION SHEET (11-15 YEARS)

PART 1 - This section should help to give you first thoughts about the project.

Title of study: Health-related quality of life (HRQL) in children and adolescents with encephalitis

We are asking if you would take part in a research project to find the answer to the question, whether problems after having encephalitis impact on the health related quality of life of children and young people.

Before you decide if you want to join in it is important to understand why the research is being done and what it will involve for you. So please consider this information sheet carefully. Talk about it with your family and friends if you want to.

Why are we doing the study?

Having encephalitis as a child or adolescent can have an enormous impact on you, as well as your family and friends. Some, but not all, young people who have had encephalitis can have difficulties such as memory problems and problems planning and organising, and controlling their feelings and behaviour. This study aims to investigate whether there is a relationship between these difficulties and health-related quality of life for children and adolescents who have had encephalitis.

Why have I been invited to take part?

You have been invited to join our study because you have had encephalitis and you can help us to understand more about whether having encephalitis when you are a child or adolescent affects your quality of life.

Do I have to take part?

No. It is up to you. If you do, I will ask you to sign a form giving your permission. You will be given a copy of this information sheet and your signed form to keep. You are free to stop taking part at any time without giving a reason. If you decide to stop, this will not affect the care you receive. Your parent/carer has also been given an information sheet and will be asked to give consent for you to be included in the study also.

What will I be asked to do?

All I ask that you do is sign the form attached to this sheet, if you are happy to be included in the study. I will be asking your parents/carers to answer some questions about you and when you had encephalitis, for example, how old you were, what treatment you had and for how long. I will then ask your parent/carer to send the questionnaires back in a stamped addressed envelope. You will not be asked to complete any questionnaires yourself.

What are the possible benefits of taking part?

We cannot promise the study will help you individually but the information we get might help treat and support young people with encephalitis in the future.

Thank you for reading so far – if you are still interested, please go to Part 2

PART 2 - More detail – information you need to know if you still want to take part.

What will happen to the information that I give to you?

We will keep your information in confidence. This means we will only tell those who have a need to know. Wherever possible, we will only send out information that has your name and address removed.

Who is organising and funding the research?

The organisers of this project will pay (University of Lincoln) for the postage costs for your parent/carer to return the forms and questionnaires.

Who has reviewed the study?

Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. Your project has been checked by an NHS Research Ethics Committee and the University of Lincoln Psychology Ethics Committee

What if I have any questions about the study?

If you have any other questions about any the study you can talk to your family or please contact me and I will do my best to answer your questions (contact number).

Thank you for taking the time to read this information sheet. If you are happy to be included in the study please sign the assent form included and pass on to your parent/carer.

Emily Talbot

Address

Trainee Clinical Psychologist

Appendix E

(Version 2: 29th January 2009)

(Letter printed on University headed paper)

CONSENT FORM

Title of Project: Health related quality of life of children and adolescents following encephalitis

Name of Researcher: Emily Talbot, Trainee Clinical Psychologist

Please initial box

1. I confirm that I have read and understand the information sheet dated 29th January 2009 (Version 2) for the above study. I have had the opportunity to consider the information, and have been given the details to contact the researcher should I have any queries regarding this.

2. I understand that mine and my child's participation is voluntary and that we are free to withdraw at any time without giving any

reason, and without the medical care or legal rights of my child and myself being affected.

3. I understand that relevant sections of my child's medical notes and anonymised data collected during the study, may be looked at by individuals from the University of Lincoln, from regulatory authorities or from the NHS Trust, where it is relevant to me and my child taking part in this research. I give permission for these individuals to have access to my child's records.

4. I agree to myself and my child taking part in the above study.

Name of child

Name of parent/carer

Date

Signature

Name of Person

Date

Signature

taking consent

Appendix F

(Version 1: 5th November 2009)

(Letter printed on University headed paper)

ASSENT FORM FOR CHILDREN/ADOLESCENTS

(to be completed by the child and their parent/carer)

Title of study: Health-related quality of life (HRQL) in children and adolescents with encephalitis

Child (or if unable, parent on their behalf) /young person to tick all they agree with:

Have you read (or had read to you) about this project? Yes No

Do you understand what this project is about? Yes No

Have you asked all the questions you want? Yes No

Have you had your questions answered in a way you understand? Yes No

Do you understand it's OK to stop taking part at any time? Yes No

Are you happy to take part? Yes No

If any answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below

Your name _____

Date _____

The researcher who sent this to you will sign this too:

Print Name _____

Sign _____

Date _____

Thank you for your help.

Appendix G

(Version 2: 29th January 2009)

DEMOGRAPHIC/ILLNESS SPECIFIC QUESTIONNAIRE

1. **Child's gender** Male Female

2. **How old is your child?** Years..... Months.....

3. **Child's ethnicity** *Choose ONE section from A to E, then tick the appropriate box to indicate your ethnic group.*

A : White

- British
- Irish
- Any other White background
(please write in)

B : Mixed

- White and Black Caribbean
- White and Black African
- White and Asian
- Any other mixed background
(please write in)

C : Asian or Asian British

- Indian
- Pakistani
- Bangladeshi
- Any other Asian background
(please write in)

D : Black or Black British

- Caribbean
- African
- Any other Black background
(please write in)

E : Chinese or other ethnic group

Not stated

Chinese

Not stated

Any other (please write in)

4. How old was your child when they contracted encephalitis?

Years.....Months.....

5. Type of encephalitis, please specify;

Infectious encephalitis (Acute Viral Encephalitis)

e.g. Herpes Simplex Encephalitis, Tick-born Encephalitis

Post-infectious encephalitis (Acute Disseminated

Encephalomyelitis) e.g. ADEM

Other autoimmune encephalopathy (e.g. Rasmussen's)

Other; please specify

Cause specified as 'unknown'

Not sure

6. Did your child receive the anti-viral medication Acyclovir at the time of their encephalitic illness?

Yes No

Not sure

7. If yes, how long did they receive Acyclovir for? (please specify in days where known or mark box if not sure)

.....
Not sure

8. Has your child received a diagnosis of epilepsy since their encephalitic illness?

Yes No

9. Did your child have any pre-existing chronic health or developmental conditions before their encephalitis illness? (e.g. developmental delay, visual/hearing impairment, epilepsy, acquired head injury); please specify;

.....
.....
.....

10. Has your child developed any chronic health conditions since their encephalitic illness (e.g. visual/hearing impairment, epilepsy); please specify;

.....
.....
.....

11. Whilst this study will not specifically be investigating sleep difficulties following encephalitis in childhood, it can be identified as a problem for some children/young people. In order to gain an idea of the number of children/young people that this may affect, please could you indicate whether your child has experienced sleep difficulties following their encephalitic illness (for example difficulties getting to sleep, disturbed sleep pattern etc.)?

Yes No