Mortality and causes of death in children referred to a tertiary epilepsy center – Danish study

Sabine Grønborg[1] & Peter Uldall[2]

[1]Center for Rare Diseases, Department of Clinical Genetics & [2]Pediatric Neurology, Department of Pediatrics and Adolescent Medicine, Juliane Marie Center, University Hospital Copenhagen

Autumn Meeting of the Danish Epilepsy Society, 24 October 2014

Background

- Children with epilepsy have a 5 – 9 times increased risk of death
- Limited data and limited awareness in pediatric setting*
- Increased mortality due to:
    - systematic complications to neurodisability
    - lethal underlying conditions
    - directly seizure related deaths, including
    - SUDEP
- Unevenly distributed mortality risk depending on different patient characteristics – “at risk populations”

Motivation for study

- Better knowledge and data regarding mortality risk and patient risk factors needed for
  - adequate and individualized counseling of families
  - future evaluation of prophylactic measures
  - better understanding of SUDEP risk and pathogenesis
  - development of general counseling guidelines

Case history (mortality risk?)

- First child, healthy parents; normal pregnancy and birth
- From the 2nd day of life:

  bursts of myoclonic seizures, partly with apnea

  followed by tonic seizures in axial and proximal muscles

  EEG with burst-suppression
- No clear effect of multiple AED and ketogenic diet
- At 2 years of age:

  daily seizures as epileptic spasms with tonic component
- Severely delayed psychomotor development

Case history - continued

- Severe, neonatal epileptic encephalopathy
- Initial diagnostic efforts without specific results

Case history - continued

- Severe, neonatal epileptic encephalopathy
- Initial diagnostic efforts without specific results

ⓘ Adequate counseling regarding mortality risk? Epilepsy-related mortality risk?

Case history - continued

- Severe, neonatal epileptic encephalopathy
- Initial diagnostic efforts without specific results

ⓘ Adequate counseling regarding mortality risk? Epilepsy-related mortality risk?

- Diagnosed with *KCNQ2*-related epileptic encephalopathy at age 2.5 years
- Found dead in bed shortly after – probable SUDEP

Weckhuysen S et al, Neurology 81: 1697, 2013

Danish Study

Original article

Mortality and causes of death in children referred to a tertiary epilepsy center

*Sabine Grønborg**, *Peter Uldall*

Danish Epilepsy Center Filadelfia, Children's Department, Kolonivej 1, 4293 Dianalund, Denmark

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 18 (2014) 66–71

Danish Epilepsy Center Filadelfia, Children's Department

Study and cohort

- Cohort: all children referred to Danish Epilepsy Center Dianalund from January 1, 1999 to August 31, 2008
  - epilepsy diagnosis confirmed after evaluation
  - age 1 month – 18 years at time of enrollment
  - cases of death registered until June 1, 2009
- Retrospective analysis of mortality and causes of death

- Cohort: 1,974 epilepsy patients - 11,309 patient years
  male:female – 1 : 0.92
  average age 15 at end of study period

Results: Overall mortality

- 43 of 1,974 patients died during the study period (2.2%)

  = 38 cases per 10,000 patient years; 2/3 male
- At least 90% of deceased patients had symptomatic epilepsy and intellectual disability
- Only 5% of the deceased population had idiopathic epilepsy (vs. 22% in the studied patient population; p=0.003)

Results: Overall mortality

- ✓ Comparable mortality rates in previous studies
- ✓ Pediatric epilepsy patients without neurological deficit – mortality close to background population

Berg AT et al, 2013. Pediatrics 132: 124-31.

Progressive neurodegenerative conditions

- 9 patients died in the course of a progressive neurodegenerative condition (8 cases per 10,000 patient years)
- Corresponding to 20% of mortality in this study, only 1 death epilepsy related

Table 2 – Patients with death in the course of progressive neurodegenerative disease.

Pt. no.	Sex	Age at death (years)	Cause of death	Therapy	Seizure control	Neurodegenerative disease
10	f	8	Respiratory insufficiency	TPM, CLB, KD	Resistant	Late infantile neuronal ceroid lipofuscinosis
11	f	20	Cachexia	VPA, LEV, CLB, CZP	Resistant	Lafora body disease
12	m	0.5	Status epilepticus/liver failure	LEV, ZNS	Resistant	Suspected adenylosuccinate lyase deficiency[a]
13	f	11	Necrotizing pancreatitis	STM, CLB	Resistant	Late infantile neuronal ceroid lipofuscinosis
14	f	2.5	Respiratory insufficiency	VPA, VGB, CLB	Resistant	Adenylosuccinate lyase deficiency
15	m	21	Gastrointestinal bleeding	LEV, LTG	Resistant	Late infantile neuronal ceroid lipofuscinosis
16	m	9.5	Respiratory insufficiency	VPA, LTG	Resistant	GM2 ganliosidosis
17	f	21	Respiratory insufficiency	LTG, CLB, CZP	Resistant	Mucopolysaccharidosis III
18	m	3	Respiratory insufficiency	CBZ, CZP	Resistant	Unclassified progressive

m: male, f: female; Epilepsy was classified as symptomatic in this patient group. None of the patients underwent autopsy. Patients 10, 16, and 17 had pneumonia leading to respiratory insufficiency.

[a] Brother to patient 14; Therapy: see Table 1.

Progressive neurodegenerative conditions

- ✓ Sparse information on neurodegenerative conditions contributing to mortality in pediatric epilepsy patients in the literature
- ✓ Mortality primarily due to complications of neurodegeneration
- ✓ Thorough initial neuropediatric evaluation in this study

SUDEP

- Death of 9 patients was classified as SUDEP (8 cases per 10,000 patient years)
- Corresponding to 20% of mortality in this study

Table 1 – Patients with death classified as SUDEP.

Pt. no.	Sex	Age at death (years)	Circumstances of death	Autopsy	Epilepsy etiology	Therapy	Seizure control	Intellectual disability
1	m	17	In bed/not observed	Yes	Symptomatic	VPA, STM	Resistant	Yes
2	m	24	Not observed	No	Symptomatic	LTG, VPA	Resistant	Yes
3	m	12	In bed/not observed	No	Symptomatic	VPA, CLB, CBZ	Resistant	Yes
4	m	8	In bed/not observed	No	Cryptogenic	VGB, LEV, KD, VNS	Resistant	Yes
5	m	20	In bed/not observed	Yes	Cryptogenic	LTG, TPM	Resistant	No
6	f	22	In bed/not observed	No	Idiopathic	LEV, TPM, ESM	Resistant	No
7	m	14.5	Cardiac arrest after focal seizure	Yes	Epileptic encephalopathy	STM, LTG, VNS	Resistant	Yes
8	m	17	Not observed	Yes	Cryptogenic	–	Rare seizures	Yes
9	m	2.5	In bed/not observed	Yes	Cryptogenic	TPM, CLB, KD	Resistant	Yes

m: male, f: female; autopsy findings: see text; Therapy: treatment with AED (abbreviated as follows: valproic acid, VPA; sulthiame, STM; lamotrigine, LTG; clobazam, CLB; carbamazepine, CBZ; vigabatrin, VGB; levetiracetam, LEV; topiramate, TPM; ethosuximide, ESM; zonisamide, ZNS; clonazepam, CZP; oxcarbazepine, OXC; pregabalin, PGB), ketogenic diet (KD), vagus nerve stimulator (VNS); Seizure control: see text; Intellectual disability: IQ $<$ 70: yes, IQ $>$ 70: no.

SUDEP

- ✓ SUDEP incidence higher than previously published (up to 4.3 per 10,000 patient years) – biased cohort
- ✓ Other studies exclude certain symptomatic epilepsies
- ✓ 4 SUDEP cases in the pediatric age group (2.5, 8, 12, 14.5 years) – although peak age is 20-40 years
- ✓ All patients with known SUDEP risk factors (GTCS, AED polytherapy, treatment resistance, …)

Various other causes of death

- 25 patients died of various reasons other than SUDEP or neurodegenerative conditions (22 cases per 10,000 patient years)
- Corresponding to 58% of the mortality in this study

- Median age at death 10.5 years (1.5 – 23 years)
- Symptomatic/cryptogenic epilepsy etiology in 24/25 patients
- > 90% with intellectual disability; 65% with motor disability
- 85% treatment resistant epilepsy

Various other causes of death

Table 3 – Patients with death of other causes.

Pt. no.	Sex	Age at death (years)	Cause of death	Epilepsy etiology	Therapy	Seizure control	Intellectual disability
19	f	3.5	Gastrointestinal	Symptomatic	CLB, VPA	Resistant	Yes
20	f	4	Pneumonia	Symptomatic	CLB, VPA	Resistant	Yes
21	f	15	Cachexia/unknown	Symptomatic	CLB, VPA	Resistant	Yes
22	f	17	Pneumonia	Symptomatic	CLB, VPA, OXC, KD	Resistant	Yes
23	m	17.5	Respiratory insufficiency	Symptomatic	LTG, STM, CLB, VGB, KD	Resistant	Yes
24	f	2	Pneumonia	Symptomatic	LEV, VGB, CBZ, KD	Resistant	Yes
25	m	11.5	Pneumonia	Symptomatic	VPA, CLB, TPM, KD	Resistant	Yes
26	m	15	Pneumonia	Symptomatic	LTG, CLB, TPM, VGB, KD	Resistant	Yes
27	m	15	Pneumonia	Symptomatic	TPM, CBZ	Resistant	Yes
28	f	4.5	Respiratory insufficiency	Symptomatic	TPM, LEV, KD	Resistant	Yes
29	m	18	Unknown	Symptomatic	LTG, LEV, CLB	Resistant	Yes
30	m	3.5	Seizure-related strangulation	Symptomatic	LTG, VPA, CLB	Resistant	Yes
31	m	23	Suicide	Cryptogenic	LTG	Seizure-free	No
32	m	2	Increased intracranial pressure	Symptomatic	LTG	Resistant	Yes
33	m	18	Increased intracranial pressure	Symptomatic	LTG, OXC	Resistant	Yes
34	f	1.5	Status epilepticus	Idiopathic	VPA, STM	Resistant	Yes
35	m	6.5	Status epilepticus	Cryptogenic	VPA, STM, PGB, VNS	Resistant	Yes
36	m	10.5	Pneumonia	Symptomatic	CBZ, VPA	Resistant	Yes
37	m	3	Respiratory insufficiency	Symptomatic	LTG	Resistant	Yes
38	m	16	Gastrointestinal	Symptomatic	OXC	Resistant	Yes
39	m	9	Gastrointestinal	Symptomatic	CLB	Resistant	Yes
40	f	21	Gastrointestinal	Symptomatic	VPA, LTG	Resistant	Yes
41	m	5.5	Gastrointestinal	Symptomatic	LTG	Resistant	Yes
42	m	6	Accident, not epilepsy-related	Cryptogenic	CBZ, ESM	Resistant	No
43	f	16	Complication neurosurgery	Symptomatic	VPA, CLB, TPM	Resistant	Yes

m: male, f: female; KD: ketogenic diet, Therapy: see Table 1; Intellectual disability: IQ $<$ 70: yes, IQ $>$ 70: no.

Various other causes of death

- ✓ Systematic complications to neurodisability are leading cause of mortality
- ✓ i.e. the underlying neurological condition itself confers substantial mortality risk
- ✓ Focus on prevention of these complications (infections, supportive care, tube feeding)

Other seizure-related deaths

- 3 deaths due to status epilepticus; 1 seizure-related accident
- Without SUDEP, only 9% directly epilepsy-related deaths

✓ Lower risk for seizure-related deaths than in previous studies

- Follow-up period

✓ No cases of seizure related drowning

- Pediatric setting

- Focused education program at Epilepsy Hospital

✓ No seizure-related deaths in patients with well-controlled epilepsy syndromes

Issue: duration of follow-up

- Study with 40 years follow-up of childhood-onset epilepsy patients (Sillanpää and Shinnar 2010 and 2013)
  - Higher overall and epilepsy-related mortality compared to studies with shorter follow-up; e.g. SUDEP in 9% of cohort
  - In idiopathic epilepsy patients mortality rate increases in young adulthood

Sillanpää M and Shinnar S. 2013. Epilepsy and Behaviour 28: 249-55

Conclusions from the Danish study…

- Mortality rates in line with previous comparable studies
- Even though SUDEP peak age is 20-40 years, pediatric age SUDEP is an important issue, also for counseling
- General risk factors comparable to adult epilepsy population
- Only 30% of mortality is directly epilepsy-related and complications to neurological disability are an important risk factor – important for general patient care

… and general considerations

- Regarding counseling - individual patient risk in patients with "complicated" or "uncomplicated" epilepsy has to be considered

- Certain SUDEP risk factors (e.g. childhood onset epilepsy, long epilepsy duration) and SUDEP peak age beginning at 20 years

  ➔ special attention to transition time from neuropediatrics to neurology

Other individual risk factors?

- Our patient case with *KCNQ2*-related epileptic encephalopathy – autonomic dysfunction reported in other patients

  ➔ possible additional counseling issue

- Genetic risk factors?
  - LongQT syndrome with seizure phenotype (*KCNQ1*, *KCNH2*, *SCN5A*)
  - Dravet syndrome/GEFS+ (*SCN1A*), and others
- Analysis of genetic variation in these and other neurocardiac genes – future biomarkers with clinical significance for SUDEP?

Glasscock E. Epilepsy and Behaviour, 2013; Massey CA et al, Nat Rev Neurology, 2014; Klassen TL et al, Epilepsia, 2014.

Acknowledgments

Rikke S. Møller and Helle Hjalgrim –

Research Unit at the Danish Epilepsy Center, and

Danish Epilepsy Center, Dianalund, Denmark

Further references

Nashef L et al, 2012. Epilepsia 53 (2): 227-33

Berg AT et al, 2010. Epilepsia 51 (4): 676 - 85

Meyer S et al, 2010. J Paediatr Child Health 47 (6): 326-31

Camfield CS et al, 2002. Lancet 359 (9321): 1891-5

Ackers R et al, 2011. Drug Saf 34: 403-13

Sillanpää and Shinnar, 2010. N Engl J Med 363 (26): 2522-9

Nesbitt V et al, 2012. Dev Med Child Neurol 54 (7): 612-7

Weber P et al, 2005. Acta Paediatr 94 (5): 564-7

Nashef L and Ryvlin P, 2009. Neurol Clin 27 (4): 1063-74

Terra VC et al, 2011. Arq Neuropsiquiatr 69 (5): 766-9

Hesdorffer DC et al, 2011. Epilepsia 52 (6): 1150-9

Shorvon S and Tomson T. 2011. Lancet 378 (9808): 2028-38