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Original article

Risk and risk factors for epilepsy in shunt-treated children with hydrocephalus

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ABSTRACT

Object: Epilepsy is a major comorbidity in children with hydrocephalus (HC) and has a serious impact on their developmental outcomes. There are variable influencing factors, thus the individual risk for developing epilepsy remains unclear. Our aim was to analyse risk factors for developing epilepsy in children with shunted HC.

Methods: A retrospective, single-centre analysis of 361 patients with the diagnosis of HC was performed. Age at HC diagnosis, shunt treatment, development of epilepsy, epilepsy course, and the aetiology of HC were considered. The influence of shunt therapy, including its revisions and complications, on the development of epilepsy was investigated.

Results: One-hundred forty-three patients with HC (n = 361) had a diagnosis of epilepsy (39.6%). The median age at the first manifestation of epilepsy was 300 days (range:1–6791; Q1:30, Q3: 1493). The probability of developing epilepsy after HC decreases with increasing age. The most significant influence on the development of epilepsy is that of the HC itself and its underlying aetiology (HR 5.9; 95%-CI [3–10.5]; $p < 0.001$). Among those, brain haemorrhage is associated with the highest risk for epilepsy (HR 7.9; 95%-CI [4.2–14.7]; $p < 0.01$), while shunt insertion has a lower influence (HR 1.5; 95%-CI [0.99; 2.38]; $p = 0.06$). The probability of epilepsy increases stepwise per shunt revision (HR 2.0; $p = 0.03$ after 3 or more revisions). Five hundred days after the development of HC, 20% of the children had a diagnosis of epilepsy. Shunt implantation at a younger age has no significant influence on the development of epilepsy nor does sex.

Conclusion: Children with HC are at high risk for developing epilepsy. The development of epilepsy is correlated mainly with HC's underlying aetiology. The highest risk factor for the development of epilepsy seems to be brain haemorrhage. The age at shunt implantation appears to be unrelated to the development of epilepsy, while structural brain damage at a

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young age, shunt revisions and complications are independent risk factors. The onset of epilepsy is most likely to take place within the first 500 days after the diagnosis of HC.

1. Introduction

Hydrocephalus (HC) is caused by increased intracranial pressure brought about by an overproduction or malresorption of cerebrospinal fluid (CSF), the mechanical obstruction of the communicating liquid drainage systems, or a combination of these factors.[1] Congenital HC has an incidence of 0.59–1.1 per 1000 live births[2,3] and can be caused by various aetiologies. Dysraphic syndromes such as meningomyeloceles, fossa posterior malformations, aqueductal stenosis or cysts are the main entities present in congenital HC.[4] HC is also a consequence of acquired disorders such as intracranial haemorrhages, tumours or infections.[1]

Seizures are a common co-morbidity in children with HC. They can occur as a symptom of an acute insult, increased intracranial pressure, due to an additional underlying brain malformation or after shunt implantation.

About 30% of all children with ventriculo-peritoneal shunt implantations have recurrent seizures.[5] There are variable influencing factors, although the individual risk for developing epilepsy remains unclear. Cortical damage due to increased intracranial pressure, age at the development of HC, shunt insertion, shunt revisions, as well as complications and the underlying aetiology of HC are related risk factors for epilepsy.[6]

HC is related to a higher risk of developmental delays and cognitive and behavioural disorders. Quality of life is significantly lower in children with HC.[7] Epilepsy can be an additional negative factor for the development, intellectual outcomes and quality of life in children with HC.[8] Therefore, it is important to identify and follow up with children at high epilepsy risk carefully and treat recurrent seizures immediately to avoid drug refractory epilepsy if possible.

The aim of this study was to identify and analyse risk factors for developing epilepsy after shunt implantation in children with HC.

2. Methods

2.1. Patients

The study was designed as a non-interventional, retrospective, single-centre data analysis.

All children with an HC diagnosis at the University Children's Hospital in Frankfurt, Germany between 2004 and 2017 were included. The observation period covered from diagnosis of HC to the last available follow-up or last follow-up due to either death or end of treatment at the hospital (in- and outpatients). All data were collected from the hospital's electronic patient files. We used a strict epilepsy definition requiring the occurrence of two or more unprovoked seizures. The classifications of seizure types, epilepsies and drug resistance were based on the definitions proposed by the International League Against Epilepsy (ILAE).[9–11] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed,[12] and the study was approved by the ethics committee of the Goethe University Frankfurt, Germany.

2.2. Statistical analysis

Categorical variables were described as frequencies and percentages. Continuous variables were described via medians, with ranges and quartiles included.

Time to HC diagnosis, shunt implantation, and epilepsy manifestation were estimated using the Kaplan-Meier method. Differences in time to epilepsy manifestation were tested with univariate Cox Proportional Hazards regression analysis. The following factors were considered: sex, age at HC diagnosis, aetiology of HC, time to shunt implantation after HC diagnosis, number of shunt revisions, time when first seizures occurred, age at development of epilepsy, and epilepsy course under anticonvulsive treatment, whereby HC, shunt implantation, and epilepsy were considered to be time-depending variables.

Results were expressed as hazard ratios (HRs) with 95%-confidence intervals (95%-CI).

The statistical analysis was done via R (version 3.5.2, R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.). All tests were two-sided and p-values ≤ 0.05 were considered statistically significant.

3. Results

3.1. Hydrocephalus

Three-hundred sixty-one patients with the diagnosis of HC were identified. Two-hundred eighteen of them were male, and 143 were female. Although there were more male patients, there was no significant difference between the sexes regarding the development of epilepsy ($p = 0.28$).

The median age at development of HC was 17 days (range: 0–6353; Q1:0, Q3:644). The age at HC diagnosis differed according to the underlying aetiology (Fig. 1). Fifteen patients died during their observation periods. There was no correlation between death and shunt treatment or the development of epilepsy.

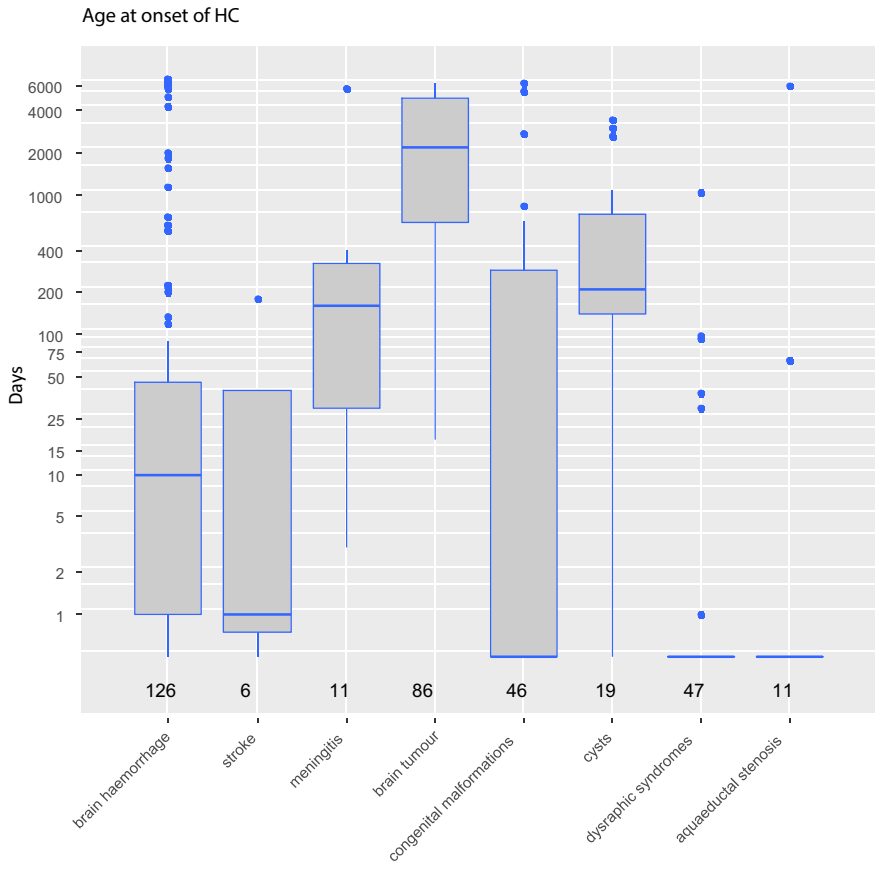

Fig. 1 – Age at first diagnosis of hydrocephalus according to aetiology.

3.2. *Aetiology of hydrocephalus*

The most frequent reason for HC in our cohort was intracranial haemorrhage (n = 126), followed by brain tumours (n = 86). Dysraphic syndromes such as meningomyeloceles, Chiari-malformations, and Dandy-Walker malformations (n = 47) or other congenital malformations such as craniosynostosis or complex brain malformations (n = 46) were common aetiologies for HC as well. Less frequent diagnoses were brain cysts (n = 19), aquaeductal stenosis (n = 11), meningitis (n = 11) or ischemic stroke (n = 6). In 5 patients, no aetiology for hydrocephalus could be identified, and in 3 cases, the aetiology was not documented (Table 1). The age at first diagnosis of hydrocephalus according to aetiology is summarized in Fig. 1.

3.3. *Hydrocephalus, shunt treatment, and epilepsy*

The median observation period was 1812 days (range 1–10,591 days). During this time, 143 of all patients with HC (n = 361) had a diagnosis of epilepsy (39.6%). The median age at the first manifestation of epilepsy was 300 days (range 1–6791; Q1:30, Q3:1493]. The probability for developing epilepsy after HC decreased with increasing age (Fig. 2).

Not all patients needed permanent CSF drainage. In some patients, HC was compensated after the acute insult or intercurrent liquor drainage by Rickham reservoirs or external liquor drainage. HC did resolve without further intervention especially in patients with transient malresorption (mainly due to brain haemorrhage) or after tumor resection. Shunts were implanted in 299 of 361 patients. The number of shunt insertions and development of epilepsy according to the underlying aetiologies are summarized in Table 1. The median age at shunt treatment was 167.5 days (range 0–6353; Q1:20, Q3:1958). Shunt implantation at a younger age (<30 days versus ≥30, respectively <200 versus ≥ 200 days) has no significant influence on the development of epilepsy (<30 days: p = 0.17; <200 days: p = 0.14). The complex correlation between the age at epilepsy onset in relation to age at shunt implantation is demonstrated in Fig. 3.

One hundred forty-three patients developed recurrent seizures. Of those, 126 had a shunt implantation. Thirty-nine patients with shunt implantation developed epilepsy before shunt treatment (pre-shunt epilepsy), and 85 of these 143 patients were diagnosed with epilepsy after the shunt treatment (post-shunt epilepsy). Seventeen of 361 patients with HC developed seizures without being treated with a shunt during their observational time. In 2 patients, the start of epilepsy was not well documented, so the epilepsy could not be related to the time of shunt insertion [the flowchart (Fig. 4) should be located here].

Finally, 500 days after the development of HC, 20% of the children had a diagnosis of epilepsy. The cumulative probability for epilepsy is shown in Fig. 5.

Table 1 – Different aetiologies of hydrocephalus and aetiology-dependent occurrences of epilepsy.

Aetiologies	total (n)	shunt (n)	epilepsy (n)	epilepsy (%)	epilepsy and shunt treatment (n)	epilepsy and shunt treatment (%)
brain haemorrhage	126	99	73	57.9	62	49.2
brain tumour	86	85	14	16.3	14	16.3
dysraphic syndromes	47	41	15	31.9	14	29.8
congenital malformations[a]	46	27	15	32.6	13	28.3
cysts	19	17	3	15.8	3	15.8
meningitis	11	10	8	72.7	8	72.7
aquaeductal stenosis	11	10	8	72.7	7	63.6
ischemic stroke	6	4	5	83.3	4	66.7
no structural abnormality	5	2	1	20.0	0	0.0
trauma	1	1	0	0	0	0.0
aetiology not documented	3	3	1	33.3	1	33.3
total	361	299	143	39.6	126	34.9

[a] Congenital malformations: agenesis of corpus callosum, schizencephaly, complex brain malformations, craniosynostosis.

3.4. *Shunt revisions, complications, and epilepsy*

In total, 189 patients had one or more shunt revisions. Revisions became necessary due to shunt insufficiency resulting into malfunction (n = 83), infections (n = 17), bleeding (n = 4) or a combination of insufficiency and infection or bleeding (n = 50). In addition, 35 patients had shunt revisions unrelated to complications, for example, a change from a Rickham reservoir to ventriculoperitoneal shunting. Epilepsy occurred in 13 of those patients, whereas 79 patients developed epilepsy after shunt revisions due to complications. The difference between the groups was not significant. Epilepsy frequency was not related to complication type. Most of the children had one (n = 64) or two revisions (n = 51). However, 31 patients had five or more revisions.

3.5. *Epilepsy risk factors in children with hydrocephalus and a shunt*

The HC is strongly correlated with the development of epilepsy (HR 5.9; 95% CI [3–10.5]; p < 0.001).

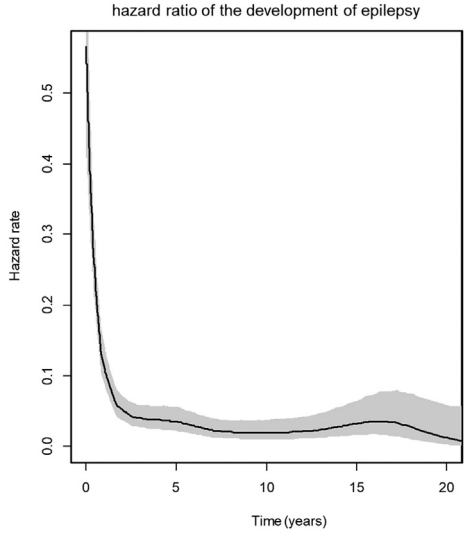

Fig. 2 – Age dependent risk for epilepsy in hydrocephalic children (with 95% confidence bands).

Among the observed aetiologies, HC caused by brain haemorrhage is associated with the highest risk for developing epilepsy (HR 7.9; 95%-CI [4.2; 14.7]; p < 0.01).

Shunt insertion has less of an influence (HR 1.5; 95%-CI [0.99; 2.38]; p = 0.06). The probability of developing epilepsy increases stepwise per shunt revision. The hazard ratio for developing epilepsy after a first and second shunt revision is HR = 1.7 (95%-CI [1.08; 2.69]; p = 0.02); after three or more revisions, the HR increases to 2.0 (95%-CI [1.0; 3.78]; p = 0.03).

3.6. *Treatment of shunt-related epilepsy and cognitive outcomes*

Data on an epilepsy course and treatment for at least one year of follow-up was available for 102 of 143 patients with epilepsy. Of those 102 patients, 23 became seizure free, and 79 developed drug refractory epilepsy. There was no significant difference in the treatment response to the epilepsy onset being before or after shunt implantation.

The cognitive outcome was documented in 156 of 361 patients with hydrocephalus. Mental retardation was described in 123 patients. Of those, 70 had a diagnosis of epilepsy. Behavioural disorders were documented in 106 patients, of whom 61 had epilepsy.

4. Discussion

Epilepsy is a major comorbidity in children with HC and shunt treatment.[13,14]

In our cohort, the diagnosis of epilepsy was confirmed in 143 of 361 patients with HC. Shunt treatment was initiated in more than 80% of all patients with epilepsy. The risk for developing epilepsy was correlated to the underlying aetiology. The highest prevalence of epilepsy was in children with HC acquired as a result of brain damage, due mainly to meningitis, stroke or brain haemorrhage. Epilepsy occurred in about two-thirds of these patients, perhaps indicating that structural brain damage is the reason for the development of epilepsy rather than the HC itself. Epilepsy turned out to be drug resistant in the majority of our patients. Developmental dysraphic brain malformations showed a low incidence of

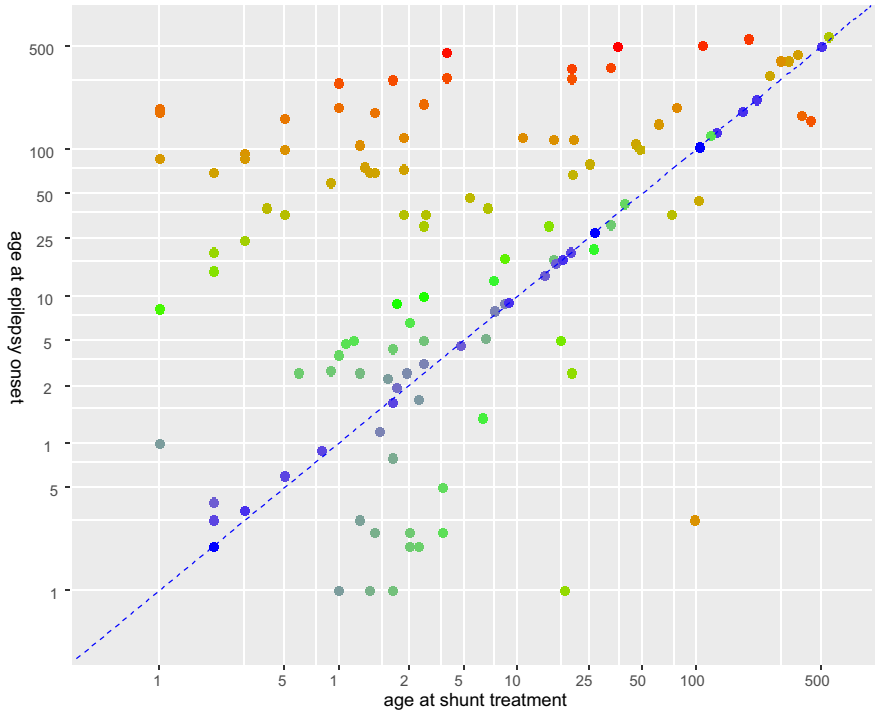

Fig. 3 – Age at epilepsy onset in relation to age at shunt implantation. Dotted line: age at shunt implantation. Points below this line indicate patients with epilepsy onset before shunt implantation (pre-shunt epilepsy), points above indicate epilepsy onset after shunt implantation. The greater the distance between the points and the dotted line, the longer the time between shunt implantation and the onset of epilepsy was.

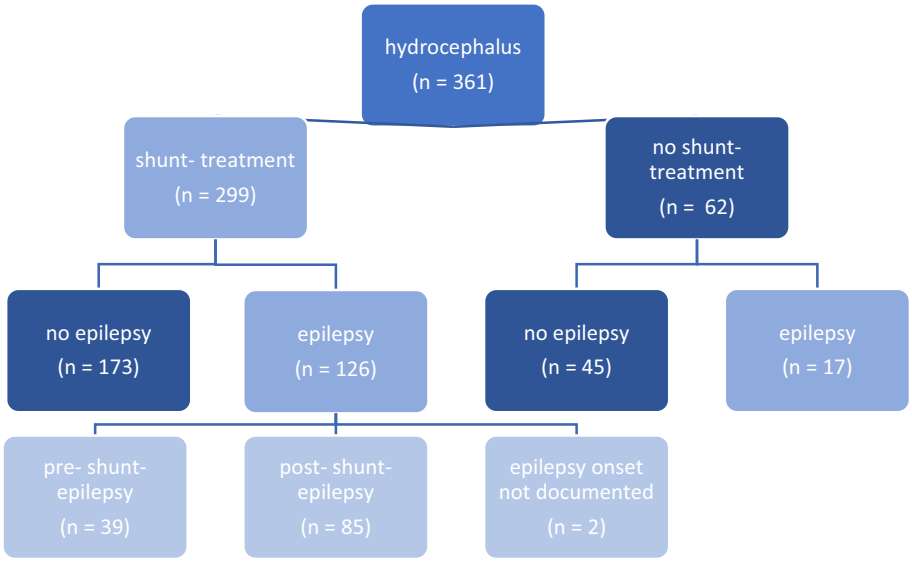

Fig. 4 – Patient cohort, shunt treatment and occurrence of epilepsy.

epilepsy, as has been demonstrated before.[4] There were only a small number of spina bifida patients in our study, perhaps explaining the relatively high incidence of epilepsy. In our cohort, epilepsy occurred in about 75% of all patients with aqueductal stenosis. It is known that congenital aqueductal stenosis can be associated with genetically determined disorders of neuronal migration and axon guidance as well as additional mid-hindbrain malformations.[15] Although genetic testing was not performed in our patients, other authors have showed that HC associated with aqueductal obstruction is early in onset and associated with the greatest severity of ventricular dilation; therefore, it has the worst developmental outcome.[4] Epilepsy was rare in children with HC due to brain tumours. HC is associated with either fast-growing malignant

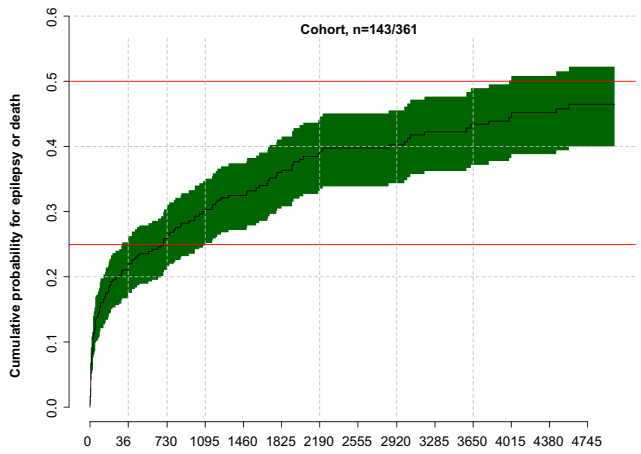

Fig. 5 – Cumulative probability for the development of epilepsy with 95%-confidence bands bands.

brain tumours or infratentorial tumours obstructing the third or fourth ventricles. A recent study showed lower incidences of epilepsy in both tumour entities.[16]

There is clear evidence that additional cortical malformations are responsible for the recurrent seizures rather than the associated HC in a select group of patients with complex brain malformations, indicating that hydrocephalus itself, although provoking symptomatic seizures due to increased intracranial pressure, does not necessarily cause structural epileptic lesions as long as it is operated on in time.

There are some controversies about the role of shunt implantation as an additional risk factor for the development of epilepsy. Some studies indicate a higher risk of epilepsy after shunt implantation.[5] There are authors who postulate better postoperative results with regards to epilepsy and developmental outcomes after a ventriculostomy as compared to ventriculoperitoneal shunting,[17,18] while others could not verify a significant difference between shunt treatment or an endoscopic third ventriculostomy.[19,20] There seem to be fewer complications and revisions after an endoscopic third ventriculostomy, but long-term outcome data is not yet available.[21] In our cohort, the latency between the diagnosis of HC and shunt implantation was usually only a few days. Since HC itself was the greatest risk factor, the role of shunt implantation itself as an independent risk factor was difficult to distinguish.

Without doubt, there is an increasing risk of recurrent seizures after shunt complications such as infections and malfunctioning equipment,[22] resulting in multiple shunt revisions.[23,24] About two-thirds of our patients developed epilepsy after shunt implantation, and less than a third had a diagnosis of epilepsy prior to shunt implantation. The probability for developing epilepsy after shunt implantation increased in a stepwise fashion per shunt revision or shunt-associated complication. In accordance with other studies, about 50% of all patients with shunt complications had a diagnosis of epilepsy.[25,26]

Age at shunt insertion and sex did not influence the risk of developing epilepsy in our cohort. Mental retardation occurred in the majority of all patients in our cohort and was frequent in patients with epilepsy. There are various studies on neurodevelopmental outcomes and quality of life in children with HC.[8,27–30] Epilepsy seems to be an independent aggravating factor leading to significantly worse intellectual outcomes[31,32] and a decreased quality of life.[33,34] Due to the retrospective design of our study, it was not possible to evaluate the quality of life in our patient cohort, but it can be assumed that the quality of life is negatively influenced by epilepsy.

4.1. *Limitations*

This study provides detailed clinical information about the aetiology of HC, shunt treatment, and the correlations to epilepsy in a large cohort of patients. However, it is limited due to its retrospective and observational character. Children with frequent hospital stays due to complications are likely to have more detailed documentation available compared to uncomplicated follow-ups. Therefore, there might be a bias towards more severely affected children, resulting in an overestimation of the prevalence of epilepsy. Additionally, shunt complications may be overrepresented. Neurocognitive data was available in only half of all patients. There may be a bias in the developmental outcome as well, as children with normal cognitive functioning and behaviour may be more often lost to follow-up.

5. Conclusions

Children with hydrocephalus are at high risk for developing epilepsy. The aim of the study was to determine the cause of epilepsy in shunted children with HC. There appears to be a multifactorial influence of risk factors on the development of epilepsy in addition to HC. The occurrence of epilepsy is highly correlated to the underlying aetiology. The age at shunt implantation seems unrelated to the development of epilepsy, while structural brain damage at a young age, shunt revisions and complications are independent risk factors. The onset of epilepsy is most likely to occur within the first 500 days after the diagnosis of HC. Since the time between HC diagnosis and shunt application was usually only a few days, epilepsy onset was more frequent after shunt implantation.

Disclosure of conflicts of interest

Susanne Schubert-Bast reports personal payments from UCB Pharma, Eisai, Desitin Pharma, LivaNova, and Zogenix outside the scope of the submitted work.

Lisa Berghaus does not state any conflicts of interest.

Natalie Filmann does not state any conflicts of interest.

Thomas Freiman does not state any conflicts of interest.

Adam Strzelczyk reports personal payments and grants from Desitin Pharma, Eisai, GW Pharma, LivaNova, Medtronic, Sage Therapeutics, UCB Pharma, and Zogenix, all outside the scope of the submitted work.

Matthias Kieslich reports personal payments from Eisai, Shire Pharmaceuticals, and Proveca outside the scope of the submitted work.

Ethical publication statement

We confirm that we have read the Journal's position on the issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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