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GENETIC EPILEPSIES IN ADULTHOOD

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TABLE OF CONTENT

1. SUMMARY

The treatment and care of adult patients with childhood-onset genetic epilepsies is an exciting area of research with many facets and potentials. In order to provide a holistic view of the challenges in the care and treatment of this patient group and the improvement potentials going forward, this thesis was structured into several chapters offering a summary of existing research results and opportunities going forward.

After a quick introduction into the topic, a dedicated chapter is describing the research methodology of literature review as the applied method and which research material was focused on.

In the next chapter of results, the different existing syndromes are described first to provide the reader with a good overview. After this there is a deeper dive into the topic of transition from childhood to adulthood.

This is followed by a dedicated look into the topics of compliance, drug related problems, psychiatric commodities and social problems, which are all of high importance in regards to childhood-onset genetic epilepsies in adults.

Based on the research results key elements such as epilepsy treatment, therapy adherence Anti-seizure medication treatment and care for social problems as well as psychological comorbidities are being discussed more further.

This is concluded in the last chapter focusing prevalent challenges and the most important factors in regard to treatment in order to achieve the best possible outcome for the patient.

2. ABBREVATIONS

ADHD: Attention deficit hyperactivity disorder

ASD: Antiseizure drugs

ASM: Anti-seizure medication

CAE: Childhood absence epilepsy

DRE: Drug resistant epilepsy

GTCS: Generalized tonic clonic seizure

HRQOL: Health-related quality of life

ILAE: International League Against Epilepsy

JAE: Juvenile absence epilepsy

JME: Juvenile myoclonic epilepsy

MAE: Myoclonic atonic epilepsy

SUDEP: Sudden unexpected death in epilepsy

3. INTRODUCTION

The aim of this master thesis is to display the challenges of treatment and care of adult patients with childhood-onset genetic epilepsies.

The etiology of the epileptic seizures is often unknown and can also be mixed (1). Epilepsy may have structural, infectious, metabolic, immune or genetic etiologies which can be acquired or inborn (2–4). If a proven genetic origin of a malformation exists, it is possible to use both terms "structural epilepsy" and "genetic epilepsy. This is for example the case with tuberous sclerosis and evidence for mutations in the specific TSC1 and TSC2 genes. Metabolic epilepsies often have a genetic origin which leads to faults in the metabolism or deficiency of biochemical agents (5).

Genetic factors are common in epilepsy (4) and play a role in about 40% (6) to 70% (7) of the cases. Pathogenic mutations in specific genes, "epilepsy genes", are a frequent cause of epilepsy (1). Genes encode proteins which modify synaptic and other cellular functions or ion channels (8). In many syndromes the exact genes are not identified (4) and in several syndromes a genetic etiology is probably the case but the fact that one syndrome can be produced through different genetic causes (genetic heterogeneity) or one gene can cause epilepsies with different types of seizures and comorbidities (pleiotropy) (9) makes the research challenging (10). One example for such a syndrome is epilepsy with eyelid myoclonia, which is usually a life-long disorder, persisting into adulthood (11) with a high probability of inheritance, but till nowadays no specific genes were found (12).

The term "epileptic or developmental encephalopathies" describes an epileptic disorder, for example the Dravet syndrome, where the seizure activity itself leads to progressive damage of the brain and produces dysfunction and deficits in the cognitive and social abilities of the patient (13). They can be acquired or genetic (1). Usually the patients become severely developmentally and cognitively disabled as they transition from childhood to adulthood (1). In recent years the greatest genetic discoveries were made in the field of these developmental and epileptic encephalopathies (DEEs).

The target of this master thesis is to investigate which aspects influence treatment success and quality of life of patients affected by of childhood-onset genetic epilepsies which begin in most cases in childhood and persist into adulthood and have a clear genetic etiology.

Furthermore, I want to evaluate factors which influence the course of the syndromes.

4. METHODS

In order to analyze which aspects are important and challenging in the treatment and care for adult patients affected by childhood-onset genetic epilepsies, a literature review was done.

I used a qualitative research strategy in form of a narrative research. My criteria were the relevance and timeliness of the articles. To achieve this goal, I concentrated especially on articles published after 2018 and I used the web side of the center for evidence-based medicine and “pubmed”.

I concentrated first on studies which discussed problems of treatment of epileptic patients in general, then I evaluated which problems are relevant for my study question and the patients with genetic epilepsy. After this, I focused on problems which are specific for adult patients with childhood-onset genetic epilepsy.

5. RESULTS

5.1 SYNDROMES

The **Dravet syndrome** is a rare DEE and is caused by de novo SCN1A gene mutations, but also mutations in other genes, (e.g., PCDH19, GABRA1, GABRG2, HCN1, KCNA2 or SCN1B) have been described (14). It presents itself in a variety of phenotypes and severity which also changes during age of the patient (15,16). Genetic causes and epigenetic factors influence the cause of the syndrome (17). The classic Dravet syndrome appears with the typically presentation of the syndrome whereas the borderline Dravet syndrome lacks absences and myoclonic seizures (15). It has to be considered that there are contrary opinions if the term borderline Dravet syndrome should be used, because the syndrome already includes a big variety of phenotypes (18).

The children affected by Dravet syndrome develop normally before the onset of the first seizures (19). After onset of the seizures, the children become impaired in their cognitive abilities and mental retardation is observed (16,20). The degree of severity varies, but the cognitive long-term outcome is often very poor (17,21). The decrease of normal cognitive performance becomes often evident in the second year of life (22) and no further cognitive development with achieving new skills is often observed after the age of five years. With increasing age of the patient, the discrepancy of normal cognitive development related to the patients age becomes more visible (21). Besides the cognitive impairment, also the

psychomotor abilities are decreasing and the patients show signs of pyramidal signs, ataxia and specific gait (23).

The seizures in Dravet syndrome begin typically in the first year of life, most often between the fifth and eight month after birth (24). They usually have consistence over the whole life of the patient (24). Brunklaus et al. discovered that vaccinated children have an significant earlier seizure onset (22).

The seizures present themselves often for first time in relation to fever of the child and are often tonic-clonic seizures or hemiclonic jerks. Early seizure onset can be a sign of a severe genotype with worse long-term outcome and decreased quality of life (25).

Furthermore, the seizures can also present themselves as myoclonic seizures, atonic seizures, focal seizures or atypical absence seizures which later also occur without fever (24) and often recur in weekly time intervals. Also, tonic seizures can be observed, which usually develop later in childhood and are not so common (24). In exceptional cases, status epilepticus can present as first clinic manifestation of the syndrome (21). Charlotte Dravet differentiated three stages of the syndrome: First the febrile or diagnostic stage in the first year; Secondly the worsening (preferred to "catastrophic") stage between one and five years, the period with frequent seizures and statuses, behavioral deterioration, and neurologic signs; and third the stabilization stage after five years in which convulsive seizures decrease and occur mainly in sleep, myoclonic and absence seizures can disappear, focal seizures persist or decrease; mental development and behavior tend to improve but cognitive impairment persists, although of variable degree (24). But the stabilization of the seizures is not always persistent, sometimes the seizures worsen after five years (24).

The seizures present themselves often prolonged, sometimes lasting over five minutes and status epilepticus is possible. The course of the syndrome and the seizures is often very severe and drug resistant, with about 10-20% of the children dying before reaching adulthood (26). In many cases the cause of death is status epilepticus or sudden unexpected death in epilepsy (SUDEP), but also accidents and drowning are frequent and are sometimes related to seizures (27). Furthermore also infections like pneumonia are often cause of death (15), but the number of patients reaching adulthood is increasing thanks to better possibilities of treatment. Still after reaching adulthood, death through SUDEP and status epilepticus is possible (28). Besides fever, there is also the change of body temperature due to other reasons as trigger described, for example the exposure of the body to hot water (21), as well as emotional stress and flashing

lights. Photosensitivity appears early and is often unrecognized, although it can be a sign of the severity of the disorder (29). The light sensitivity is sometimes so high, that just eye closure can lead to auto stimulation and seizures (24).

In adults with Dravet syndrome**,** sometimes an improvement of the seizures is observed after the second decade of life, respectively in some cases the seizure frequency decrease after childhood (30–32). The most dominant seizure form in adults, but less common than in children, are nocturnal generalized convulsive seizures, often with the focal onset. Other forms of seizures like atypical absences, myoclonic or focal seizures are less common in adulthood (32).

Akiyama et al. observed that all patients experienced Generalized tonic clonic seizure (GTCS) with generalized onset and more prominent clonic movements, unilateral seizures, and focal seizures with loss of awareness, eye deviation, and sometimes mild tonic posturing during their childhood and also a majority experienced convulsive status epilepticus. Also, myoclonic seizures, as well as atypical absence seizures were observed. In later course of the syndrome, the seizures improved in almost all patients and no patient of the study had a convulsive status epilepticus after the 10^{th} year of life. Even if the majority of the patients still had seizures, a small minority was in remission for over a year, not having seizures at all. In the great majority, myoclonic and atypical absence seizures had disappeared before reaching the age of 20, photo and pattern sensitive seizures had also significantly decreased (15).

The improvement of the seizures seem not necessarily to be correlated to the type of SNC1A mutation or seizure manifestation and frequency in childhood (30).

The age of seizure onset is important, because there is evidence that it is a more important factor for predicting the disorder outcome than the mutation type, especially seizure onset in the first six month or the first year after birth. It's likely that early seizure onset is related to poorer long term outcome of the patient (33) and cognitive impairment in adulthood (16).

Early intervention with high effort in seizure control in Dravet syndrome is important, especially treatment of prolonged seizures in the first year of life, to decrease the possibility of epileptic encephalopathy and improve the cognitive outcome for the patient (33,34). The seizure long-term outcome and development in adulthood seems to be positively influenced by absence or respectively aggressive treatment and prevention of convulsive status epilepticus (15). There is disagreement of the influence of the seizure length and status epilepticus for the cognitive

long-term outcome however. Some studies show that a poor prognostic factor for cognitive outcome is the early development of absences and myoclonic seizures, but not prolonged seizures and status epilepticus (17,22).

Seizures which are resistant to drug therapy are common in Dravet syndrome (23) and sodium channel inhibitors typically worsen seizures (35).

15–20% of all epilepsies are genetic generalized epilepsies. These include childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic–clonic seizures alone (36).

Juvenile myoclonic epilepsy (JME) is responsible for about 5-11% of all epilepsies and for about 18% of genetic epilepsies (37,38). In inherited form, it is autosomal dominant with change in the GABRA1 gene (39). It is usually a life-long condition, with the possibility of remission under ASMs, but the side effects of ASMs can be a reason to think about the usefulness of treatment (40). The course of the syndrome is not predictable, but age of seizure onset, severity of seizures, mutation type, drug therapy probably influence the course (16). The seizures of JME start usually in childhood or adolescence with a mean age at 14 years (41), and present themselves usually in three types of seizures: myoclonic jerks, which typically occur in the first hours after waking up and are usually bilateral but sometimes also occur unilateral and are more pronounced in the upper limbs, generalized tonic-clonic seizures which sometimes follow the myoclonic jerks after waking up, and absence seizures. The myoclonic jerks vary in intensity , from just involving the finger to strong movements leading to the fall of a person (37). Typical myoclonic jerks present first in disorder course, after some months also generalized tonic-clonic seizures appear. Further, clinical typical absence seizures are visible in about one third of the patients, which usually start in the age of five to sixteen years (37) and sometimes a tremor of the hands during neurological examination (42). The myoclonic jerks are often triggered by lack of sleep, alcohol, emotional stress and flashing lights (37). The development of a status epilepticus is a rare event and responds usually well to treatment with benzodiazepines (43). Baykan et al. discovered that on 20 years follow-up a great majority of the patients were not in total remission and were still affected by seizures. But even in cases without total absence of seizures, often the seizures improved and many patients had a timespan of at least five years with remission of the seizures (44). There is the possibility that patients have no symptoms even over decades and then the seizure come back in older age (43). Nevertheless, 16,7% of the patients didn’t respond to the treatment and had no other reason for

treatment failure, were classified as patients with true therapy resistant epilepsy (44). Risk factors for poorer outcome are the presence of all tree seizure types, systemic disorders, psychiatric problems, delay in diagnosis, treatment failure, presence of focal and atypical seizures (43).

Camfield and Camfield got similar results in a long-time follow up study after 25 years. 70 % of the patients were not in total remission. But in about one-third of the patients epileptic drug treatment was not necessary anymore due to the total absence of seizures (17%) or only myoclonus epileptic activity (13%) (45).

In contrast to other studies which state that earlier age of the seizure onset (46) is often related to more sever cognitive dysfunction (47) and especially a seizure onset age less than 16 years (41), respectively 15 years (48) are associated with poorer outcome, the findings of the study by Somnez et al. does not support this assumption (49). Furthermore, additional absence seizures seem to worsen the disorder course (48).

The long-term outcome of the development of the severity and frequency of the epileptic seizures in adults with genetic epilepsy with onset in childhood or adolescence differs considerably between the syndromes. Seizures often change in severity and frequency during age and differ in adulthood from childhood or even syndromes become other syndromes (50). Seizures differ in their clinical presentation and their origin in the brain, seizures with focal-onset are characterized with hyperexcitability of the neurons in specific parts of the limbic or cortical circuit, where the hyperexcitability in generalized epilepsies is not restricted to a localized brain part (51).

In seizures of **childhood absence epilepsy (CAE),** caused usually by de novo mutations in the genes SCN1A, SCN8A or CLCN2, the child is typically not able to respond to stimulus for about 10 to 20 seconds and stares. It is possible that the child blinks or the eyes roll up. Also chewing movements of the mouth are possible. The seizures, which usually start between the age of four to eight years typically happen multiple times a day, start and end fast, with the child not remembering the seizures. About one third do not respond to treatment and the seizures remain after mid-adolescence. Around 10-15 % of these patients develop other kind of seizures later in adolescence, so there is a high chance for children who are not going into remission to develop JME in later stages of life (52). The presence of generalized tonic-clonic

seizures (GTCS) or positive sharp waves (PSW) in EEG, side effects of ASMs and psychiatric comorbidities are observed sometimes in patients with a negative long-term outcome (48).

Although **Juvenile absence epilepsy(JAE)** and CAE are clinically separate syndromes, which are differentiated by the age of seizure onset, it is not clear if they are genetically distinct (53). It's a lifelong persisting syndrome. The seizures in juvenile absence epilepsy usually start later, in most cases between the age of nine and thirteen years, but sometimes also in advanced age. The syndrome does not have a similar benign seizure development in disorder course as the CAE does. Further next to absence seizures, which are seen in all cases and have a duration of about 10-45 seconds, about 50% till 80% develop later in life tonic-clonic seizures. The tonic-clonic seizures usually appear in awaking phase. JAE shares many similarities with JME, but the most important difference is the absence of myoclonic seizures (54). Usually seizures of JAE respond well to treatment.

The seizures of **sleep-related hypermotor epilepsy** (autosomal dominant nocturnal frontal lobe epilepsy) begin in the majority of cases before the age of 20. Very often around the age of 10. Seizure onset is described between the age from early childhood till later adulthood in general. Gene mutations in nicotinic receptor subunit genes CHRNA4, CHRNB2 and CHRNA2, as well as in potassium channel genes (KCNT1) and other genes have been described (55).

Frequent, often in one-night repeating, short hypermotor seizures during sleep are typical for this syndrome. Very often the seizures are not very impressive and seem to belong to normal sleep and dreaming behavior, lasting only some seconds, but there is also the possibility of more pronounced motor movements like twisting or turning, and grimacing or vocalization and a duration of some minutes or the development of clusters with the urge for medical intervention. Also wandering during sleep is possible. The level of awareness of the seizures of the patient varies. The seizures happen during the whole life of the patient, but usually are not progressing, decrease in intensity with age and respond well to treatment. Nevertheless, about 30% of the patients have drug resistant seizures (56).

Children with **myoclonic atonic epilepsy (MAE)** or also called **Doose syndrome** can have mutations in various genes, including SCN1A, SCN1B, SCN2A, SLC2A1, CHD2, SYNGAP1 and KIAA2022. The seizures present themselves in different types which usually take place more often in the morning: generalized tonic-clonic seizures are seen in most children, in many

cases triggered by fever. Also, myoclonic and absence seizures as well as the typical drop seizures with atony of the body, are commonly seen. A predictor of poorer outcome can be tonic seizures, which often develop later in disease course. Status epilepticus is relatively common in all seizure types. Since the seizures can also be triggered by fever, it's important to exclude the Dravet syndrome. MAE seizures usually start at the age of two years, which is later than in the typical Dravet syndrome, have the specific phenotype of the drop attacks and the syndrome course is different (24). Like other genetic epilepsy syndromes, seizures in MAE are often drug resistant. About 50% of the patients do not go into seizure remission (24). A predictor of poorer outcome can be tonic seizures, which often develop later in the disorder. Ketogenic diet, vagus nerve stimulation can be a treatment option in case of drug resistant seizures (57).

The age of first seizure onset and clinical symptoms of syndrome manifestation is an important factor for long term outcome of the syndromes. Early seizure onset, especially before the age of 13 (58) in epilepsy with generalized seizures, seems to be a predicting factor for negative long term outcome. Age of seizure onset is used to differentiate and define syndromes, like childhood and juvenile absence epilepsy, as help for differential diagnosis between different syndromes and as a potential prognosing factor, provide information about therapy planning, disease course and long-term outcome eventually. Complicated epilepsy combined with intellectual disability and uncontrolled seizures in childhood are an important prognostic factor for negative long-term outcome of the patients in adulthood (59).

5.2 TRANSITION

In the future, more children with early onset epilepsy of genetic etiology will reach adulthood and therefore will need treatment and care by an neurologist specialized for the treatment of adult patients (60).

A problem of treatment of genetic epilepsies is that there is not much information and data for long-term prognosis of many of these syndromes (61), but due to research and better therapy options, the survival rate of children with genetic epilepsies has increased (60). There is a lack of exposure of adult neurology trainees to complex childhood-onset genetic epilepsies (62). A potential challenge in treatment of childhood-onset genetic epilepsy in adults consists in finding a neurologist in adult care (63) who has the experience and confidence to treat childhood-onset genetic epilepsies in adults, especially if comorbidities are also present (20). Especially when it comes to encephalopathies and epilepsy with genetic etiology, the adult neurologist often feel

insecure (64). One example of genetic early onset epilepsy where children often enter adulthood is the Dravet syndrome (28). According to Borlot et al. adult neurologists felt only in 15,4% confident to treat adults with epilepsy and additional comorbidities and only 9,8% felt confident to treat adults with childhood-onset genetic epilepsy (65).

A majority of adult neurologists are not familiar and skilled to treat adult patients with a clear genetic mutation or genetic syndrome, because in the past patients who were able to enter adult neurological care were not so frequent (65). Due to this, treatment of adults with genetic onset epilepsy is a relatively new field for many neurologists and they have to look into it (64).

One reason for the lack of confidence in treatment of adults with childhood-onset genetic epilepsy is the lack of experience and training. As well as probably the difference in drug treatment of pediatric and adult patients. With some medications, for example "stiripentol", adult neurologist are not very familiar, because the drug has regularly been used in the pediatric population only or drugs are only produced for the pediatric market and are officially not authorized for adults (28). Furthermore, also in case if the adult neurologist is familiar with the drug the patient is treated with from childhood on, he or she has to modify the drug regime for the grown-up patient. Since in most clinical trials for ASMs the patients have a very restricted age range, it makes it more difficult for the physician to plan the drug therapy according to the specific personal need of the patient at a specific age and know the relative drug effects (28). Finally, also other treatment methods like special diets or neurostimulation being more common for seizures ,which are not well controlled by drugs, can be are reason for the lack of confidence of the adult neurologists (63).

For adults with childhood-onset genetic epilepsies there seems to exist a gap of optimal healthcare (66), because during transition from pediatric to adult care the patient experiences that the pediatric neurologist has good experience about treatment of the syndromes, but less knowledge about other factors which are challenging for epileptic patients regarding adult problems, like sexuality or daily life issues as being unable to obtain a driver's license (67), on the other hand adult neurologist are familiar with these problems, but less experienced in treating childhood-onset genetic epilepsies (67). Low quality healthcare for children during transition to adult care, can lead to interruption of treatment with worsening of the symptoms and a higher morbidity and mortality in adulthood (65,66).

Adult neurologist with good knowledge about childhood-onset genetic epilepsies are rare, hence many programs for transition from pediatric to adult care dependent on only a few

experienced physicians (63). Early cooperation between pediatric and adult neurologist are beneficial for the patient, but often economic considerations and financial restrictions in the health care system, especially for multidisciplinary programs where pediatric and adult neurologist work together, influence the transition from pediatric to adult care for patients with childhood-onset genetic epilepsy in a negatively (65).

During transition from pediatric to adult health care, the patient also goes through puberty. Puberty is a time where many changes in the body and mind occur. The activation of gonads takes place, the activation of growth factors and the adrenal axis changes. The excessive grow during puberty can lead to problems when ASMs interact with the bone and vitamin D metabolism and decreases bone density. During puberty, the brain goes through transformation. Frontal lobe executive changes happen which go along with an imbalance of control and risk taking or pleasure seeking behavior, as well as reduced assess of long-term consequences (68). Due to this, problems of compliance are common during transition.

Furthermore, because of the physical and also social changes during this period, like new family dynamics or challenges in private life and educational or professional burden, the patients are more vulnerable for psychosocial comorbidities like depression and mood disorders (50). It is important that the adult and pediatric neurologists not only put attention to the treatment of the epilepsy, but put also attention also on additional aspects like psychological needs and social problems of the patient (69).

The time after the patient has entered from pediatric care to adult care is a good time to reevaluate the diagnosis of the type of epilepsy for example by using new methods of genetic testing. Furthermore the physician should modify the therapy, identify additional needs, for example for financial or legal support and screen for psychosocial risk factors (65).

Borlot et al. describe the three possible outcomes for adult patient with childhood-onset epilepsy as followed: First a cognitive normal patient with well-controlled seizures, for example patients with juvenile myoclonic epilepsy, secondly cognitive normal patients with difficult to treat seizures and third cognitive impaired patients with uncontrolled seizures (20).

Due to the different possible cognitive and seizure outcomes of the patients with childhood-onset genetic epilepsy, the needs of the patients regarding of healthcare and additional support vary considerably. The often weak transition preparation in pediatric system, the lack of knowledge of pediatric epilepsy syndromes, and the lack of global support for patients with

intellectual disability and multidisciplinary care are a problem for the patient and neurologists (67). Patients with childhood-onset genetic epilepsy are often very complex patients for the adult neurologist (20). The adult neurologist should be aware of the needs and concerns of adult patients and prepared for the increasing proportion of patients with childhood-onset genetic epilepsies (60).

5.3 COMPLIANCE

Unfortunately, non-adherence to treatment is global problem in epilepsy treatment (70). Adherence, respectively compliance to the treatment regime is often difficult for adults (28) and declines over time (71).

Seizures which are not satisfactory controlled increase the probability of negative outcome for the patient in various aspects of life. They increase the chance for physical injury, morbidity and mortality, and also for social and mental problems (72). Further, they are a big risk factor for decreased quality of life (71). First line therapy in epilepsy is ASM, incompliance to the drug therapy can cause therefore negative long-term outcome for the patient (71). Factors which contribute to bad compliance are mood and anxiety disorders, complex medication plans, perceptions and cultural beliefs about the medication (73), bad communication and relationship between the clinician and the patient as well as the persisting presence of uncontrolled seizures (58). Fear or experience of unwanted side effects of the ASMs are also a frequent reason why patients stop the drug therapy (73).

Drug compliance is problematic for patients transitioning to adulthood (28). Stigmatization (74), pressure through the peer group, less monitoring and control by parents (75), other interests and physical changes makes it often challenging for young adults to adhere to the therapy (71). During puberty, in emotional situations the more mature limbic system wins over the less mature prefrontal cortex, which can lead to wrong decisions. Pleasure seeking behavior is often not well controlled which leads to wrong prioritization of actions and less compliance (68).

For successful transition from childhood to adulthood, it is important that the patient learns to take responsibility for his or her medication regime (28). Furthermore, the frequent cognitive and psychiatric comorbidities in genetic epilepsies starting in childhood have a negative impact on compliance (71). Also methods for therapy resistant seizures like ketogenic diet are more difficult to implement in adults than in children (28). To support the adherence to therapy of

such patients, it is recommended to find specialized care place for patients in the transitioning, for example an epileptic dietary center in case of ketogenic diet for adults (28).

A very important point for therapy effectiveness is the education and understanding of the patient and counselling interventions. Studies show positive effects of education on compliance and improved seizure development with decreased severity and frequency (76). On the other hand, there is also the positive correlation of poor compliance with lower understanding of the therapy and increased severity of frequency of the epileptic seizures. The intelligence of the patient plays a subordinate role when it comes to drug compliance (28). A higher level of compliance leads to an better outcome of the epilepsy treatment and well-being of the patient (77).

One of the most important aspects to increase the drug compliance is to implement a system of reminding the patient to take the medication. "To forget the medication" is the leading cause of non-adherence (70). Therefore the physician should try to implement a method to decrease the risk for forgetting medication intake, for example by reducing the amount of daily single doses (28,78) If the compliance of the patient is not satisfactory, the neurologist has to exclude overload of the patient or avoidance of drug therapy due to a too complex drug regime (28,73) or a discrepancy of understanding between physician and patient (79).

Another factor which plays an important role for compliance and therapy success are potential barriers and comorbidities for adherence.

The socioeconomic situation of the patient is a good predictor for therapy compliance.

There is evidence that the socioeconomic class has significant influence on the adherence to therapy (80). Patients with lower socioeconomic state have usually higher barriers to care access (73), due to their financial situation, access to infrastructure and transport possibilities (71). Still contradictory studies exist which don't support the socioeconomic class as good predictor for compliance (78).

Gutierrez-Colina et al. found out, that 81,81% of adolescence which had epilepsy from childhood on explained they had at least experienced one barrier regarding adherence to the therapy. The type of barriers were different, for example distance of the pharmacy to get medication, inadequate seizure control or forgetting to take the medication (75).

A good relationship and understanding to the reference persons and people who are involved in therapy, especially the physician, and identification of risk factors and treatment of comorbidities have a beneficial effect on drug compliance (71).
Furthermore, a therapy concept with a team of multidisciplinary therapists with experts from different specialties who can offer support in various fields can increase the adherence of the patient (71).

5.4 DRUG RELATED PROBLEMS

The most important goal in epilepsy treatment is the reduction of seizure frequency (81) combined with less possible side effects due to medication (82).

The first step in the epilepsy treatment is usually the use of ASM. First as monotherapy with one ASM, if the seizure control is not satisfactory, with an combination of drugs (83). If this therapy regime fails, reevaluation of the seizures is necessary. Further it is important to consider additional drug trials or alternative therapies like respective surgery, ketogenic diet or neurostimulation (84).

The treatment with ASMs is not successful in about one-third of the general population of epilepsy patients. These patients are not reaching the goal of total seizure freedom despite research and new generation ASMs (81).

In adult patients with genetic epilepsy, the failure of reaching seizure freedom through the use of ASMs is frequent (44,45,85). Drug resistance is a common problem in patients with epilepsy of genetic onset.

ASMs work through the influence on four main ways, they block or mediate voltage- operated calcium or sodium channels (carbamazepine, eslicarbazepine, gabapentin, pregabalin phenytoin, oxcarbazepine, lamotrigine), influence GABA- mediated processes (phenobarbital, benzodiazepines, topiramate, tiagabine, valproate, vigabatrin) or glutamate mediated events (lamotrigine, perampanel and topiramate) (86) or they modulate neurotransmitter release (levetiracetam, brivaracetam). Also several mechanisms of action are possible (51).

Drug resistant epilepsy (DRE) is defined by the International League Against Epilepsy (ILAE) as “the persistence of seizures despite at least two syndrome adapted antiseizure drugs (ASD) used at efficacious daily dose”(87). Only about 50% of patients under therapy who still have seizures are really “drug resistant” and meet this criteria, also other reasons for therapy failure are possible, due to this, precious evaluation of the treatment failure is necessary (58).

The resistance to treatment with ASMs can be caused by various reasons, unfortunately there are still in many cases a lack of knowledge about the definitive mechanisms and causes (88). In adult patients with drug resistant epilepsy, an undiagnosed Dravet syndrome should be excluded (89).

The effectiveness of an ASM dependents on the drug metabolism of the body, which includes the serum concentration of the ASM, the elimination time and drug pathway. Findings suggest that the modulation of enzymes and other molecules as well as pharmacokinetics and pharmacodynamics, are influenced by genetic variations or mutations in specific genes ("epilepsy genes") which also often correlate with specific epileptic syndromes (88).

Gene mutations which are responsible for epilepsy and often associated with drug resistance are for example genes which influence the rapid transmembrane sodium flux and due to this neuronal excitement. These genes are known as sodium channel genes, whereby mutations in the genes SCN1A and SCN2A are proven causes of epilepsy with difficult to treat seizures (90) and often recurrent status epilepticus, especially in the first years of syndrome (35).

Particularly effected of this drug resistance are for example patients with Dravet syndrome (58), where almost all patients can be designated as affected by a severe form of a pharmacoresistant epilepsy (91). Furthermore, sodium channel blockers which are usually often used in epileptic syndromes should not be used in the treatment of Dravet syndrome, because they can worsen seizure activity (14) In adults with therapy resistant seizures there is the possibility that these patients have a not diagnosed Dravet syndrome (89).

Patients with other epileptic encephalopathies or epileptic syndromes are also often affected by drug resistance (35,58). For example, in JME, the rate of long-term remission is very low. For patients with juvenile myoclonic epilepsy the right drug is important for the success of treatment. Patients with inadequate seizure control just taking drugs appropriate for focal epilepsy should not count as therapy resistant, but change medication. As in Dravet syndrome, sodium channel inhibitors should be avoided because they can exacerbate myoclonic seizures (54). Patients with therapy resistant juvenile myoclonic epilepsy have more psychiatric comorbidities (44).

Especially therapy resistance favors a multitude of comorbidities for patients with genetic epilepsy (89). These comorbidities are psychological like anxiety and depression, but can also lead to worse quality of life, cognitive decrease, physical problems and earlier death through

status epilepticus, SUDEP or other complications. Especially uncontrolled generalized tonic-clonic seizures are a risk factor for SUDEP (92). Seizures which persist into adulthood and are not well controlled, decrease the social and psychological well-being and also the behavioral and social outcome of the patient, (71) for example the risk for depression is clearly elevated. (93) Also the risk for injury and accidents is increased (92,94).

Drug therapy of drug resistant seizures commonly ends up in polypharmacy, a drug regime with use of several ASMs (58). Because of this, patients with not satisfactory controlled seizures and who are considered as having drug resistant epilepsy, should be evaluated by specialists in a tertiary center for other treatment options than ASMs, for example surgery, neurostimulation or ketogenic diet (50,58,81). Adults with childhood-onset genetic epilepsies transitioning to adulthood have a high risk for polypharmacy, because polytherapy is common for patients transitioning to adult care and the seizures are often poorly controlled (28) .

Seizures which are more difficult to control often lead to the use of a couple of medication (58), which increases the risks for unwanted drug interaction and side effect o (95). The number of medication side effects has a significant negative influence on Health-related quality of life (HRQOL) of the patients (96). Studies show that drug therapy with three or more drugs is associated with worse seizure control and decreased quality of life (95,97). Furthermore, there is a significant connection between the number of the ASMs and the decreased success of seizure control (77). Another factor which can lead to polytherapy is diagnosing psychogenic nonepileptic seizures as epileptic seizures and insufficient management of lifestyle trigger factors, for example sleep deprivation or alcohol intake (28).

The side effects of ASMs used in the therapy of adults with genetic epilepsies vary from mild to potentially harmful (88). In a cross sectional study with 809 patient which were treated with ASMs, 36% had at least experienced one adverse drug reaction (88). Unwanted side effects of ASMs contribute to non-adherence and can decrease quality of life (98). The use of antiepileptic drugs has negative influence on alertness, reactiveness and motor coordination of the patient (99). Due to this, patients treated with ASMs have a higher risk for injuries and accidents (3). Furthermore negative influence of the mood and psychical well-being of the patient (92) or behavior problems like aggression can be triggered in some patients (28). Other potential side effects especially for females can be sexual dysfunction (100) and an earlier menopause (100). Some ASMs even increase the risk of malformations of the fetus and neurodevelopmental delay of the child in case of use during pregnancy (43).

The sexual performance usually is not at the desired level for adults taking ASMs which can be induced by alteration of sexual hormones due to the drugs. But also other aspects, for example psychosocial comorbidities can contribute to this problem (67).

Bone health is an important aspect for patients with childhood-onset genetic epilepsy, because childhood and adolescence are an important time for bone development (100) and the long-term intake of ASMs over years lowers the bone mineral density (68). Lower bone mineral density is associated with higher risk of fractures in adult patients (92).

The drug valproate for example, which is the first line drug in Dravet syndrome and juvenile myoclonic epilepsy and acts by blocking of the natrium and calcium channels, is associated with nausea, vomiting, hair loss, sedation, weight gain and hyperammonemia, and also with blood dyscrasias and pancreatitis (23). In juvenile myoclonic epilepsy, side effects like weight gain, tremor, hair loss and teratogenesis, are the main reasons to treat the patients with other drugs than Valproate (43). Topiramate, used for example for treatment of Dravet syndrome, interacts with the GABA receptors. Although it has a good safety profile it can also induce weight loss, anorexia, renal stones and behavior changes (23). Stiripentol, which is used in therapy of Dravet syndrome and influences the GABA-A receptors can decrease appetite and lead to sedation. Also, it interacts with other seizure medication and can increase their concentration due to interaction with cytochrome P450. Levetiracetam which interacts with vesicle protein 2A and increases GABA can lead to irritability, aggression, depression and suicidal thoughts (92). Levetiracetam is one of the few treatment alternatives for women with Juvenile myoclonic epilepsy in childbearing age. According to the study of Mevaag et al., more than 40% of the women experienced unwanted side effects like aggression, mood changes and irritability from levetiracetam (98).

To reduce unwanted adverse reactions of drugs, more research on genetic factors which influence drug reactions and a more patient-individualized therapy seem to be useful. Although, polypharmacy should be tried to avoid if possible (88) because the side effects and risks of the ASMs are for some patients a reason to stop the drug regime (73).

5.5 PSYCHIATRIC COMORBIDITIES

Comorbidities are frequent in adults with childhood-onset genetic epilepsy (20).

They can be of physical nature, for example a crouched gait and ataxia, and also Parkinson's syndrome with its specific symptoms like bradykinesia, asymmetric rigidity and cogwheeling in some patients with Dravet syndrome (89) or of cognitive and psychological nature.

Cognitive impairment is common for neurological disorders (93). Various cognitive domains such as language skills, social skills, logic, emotion control, memory or attention can be affected (58). Young age at seizure onset is a better prognostic factor for cognitive problems than behavior disorders (65).

Psychiatric disorders like depression, anxiety or behavior problem and mood disorders (65) are common comorbidities in adults with genetic epileptic syndromes starting in childhood or adolescence (44,45,101). Children with epilepsy are commonly affected by behavior or psychiatric comorbidities like ADHD(102), anxiety, depression and autistic spectrum disorder (103), whereby the risk for ADHD is very high in children with epilepsy (93,104). Due to 19 studies the risk for ADHD was for general epilepsy 4,7%, infantile spasms 19.9%, focal seizures 41,9%, and Dravet syndrome 47,4% (105). Psychiatric comorbidities are a risk factor for true drug resistance (43).

Although in Dravet syndrome the cognitive functioning varies between individuals (16), as well as older children have usually a significant lower cognitive score than younger children(106), severe cognitive and developmental impairment is common (107). Furthermore, sleep disturbances are a frequent problem in patients with Dravet syndrome (89).

In Dravet syndrome even mild cognitive impaired patients are not able to draw a painting or write, because the hand-eye coordination is very poor, the fine motor abilities are under-developed and the patients have often segmental myoclonus (24).

The psychosocial long term outcome of juvenile myoclonic epilepsy is usually good (108), but depression can be a burden of some patients (45). In absence epilepsy, one of three patients has problems with concentration, memory performance and attention (109). If the patient also has psychiatric comorbidities the long-term outcome is poor for these patients (48).

Psychological, behavioral and social problems are common in Dravet syndrome, with a prevalence on standardized instruments ranged between 37% and 100% (106). For the best outcome for the patient, psychological disorders and social deficits and behavior problems should be identified and treated as early as possible (110).

Behavior problems and autism are also frequent in Dravet syndrome (25) but become often less severe in adulthood (111). ADHD, which is the most frequent behavior problem in Dravet syndrome (16), hyperactivity and abnormal behaviors associated with ASD are also common in patients with Dravet syndrome (16,24). Also, significant social communication deficits are common, even though often not identified (16). These problems typically persist into adulthood (16). Furthermore, mood problems like aggressiveness, irritability, relational difficulties and autism are frequently observed and influence the social outcome of the patients (23). Especially hyperactivity and ADHD influence in long-term consequences the educational success and life quality of the patients (16).

Low quality of life is a risk factor for behavior problems and in the opposite, a high HRQOL correlates with lower rates of behavior problems (106). The identification of psychological, social and behavior problem treatment and care is an essential factor in the care for patients with Dravet syndrome and may be a more important factor for quality of life than cognitive performance ability (16,25).

In adolescence, girls have a slightly increased risk for anxiety compared to boys (104). Also risky behavior and rebellious behavior is sometimes observed in adults with epilepsy, possibly due to a decreased control of emotions and cognitive function (112).

It is likely that in some cases with psychiatric comorbidities, the patient was not correctly diagnosed as a child (104) and therefore, an early intervention with effective therapy possibilities to decrease negative development of the mental health problems in the adult patient is delayed (28). The psychological and psychiatric problems typically "co-occur" in children, adolescents and adults (93).Increased seizure severity and seizure frequency are risk factors for mental problems (104). It is possible that the psychiatric problems, which are often for the patient more impairing the life quality than the seizures, are directly caused by the epilepsy (93).

Epilepsy is in general a high-risk factor for depression (93) and suicidal behavior and it has a huge impact on life quality (92). Affected people have an up to two till three times higher risk for depression (58), have more frequent suicidal thoughts and an almost three times higher risk for death because of suicide (92). Other risk factors for depression are higher body mass index, minor physical resistance and low self-esteem (67). Although thought disorders and psychosis have a negative influence on life quality and can increase the risk of death (93). Unfortunately, depression in epileptic patients is often not diagnosed, because caretakers and people of the

social environment of the patient think that the symptoms like altered sleep, fatigue and cognitive showering belong to effects of the seizures or medical treatment or the symptoms present atypical (92). Patients with epilepsy have also a two times higher risk for developing an anxiety disorder then healthy individuals (93). Besides anxiety disorder also panic disorder, social phobia, obsessive disorder and general anxiety are more often observed in people with a seizure disorder (58).

Autism has a higher prevalence when the patient is younger, has a higher level of cognitive impairment and in specific epilepsy syndromes like infantile spasms or Dravet syndrome (105).

It is important to offer the patient and the family support, inform them about therapy possibilities and decrease barriers, especially for the utilization of mental health support (16). All psychiatric comorbidities besides pharmacotherapy seem, to benefit from psychotherapy and behavior modification and require education of the patient and the environment (104).

There are not enough high quality studies regarding treatment guidelines for depression in patients with epilepsy (92). Psychological support is especially helpful (104) and improves HRQOL and comorbidities in depression and neurocognitive disturbances (113).

It is important to provide information about the risk factors for ASD in epilepsy and define the clinical guidelines for detecting patients at risk and also to implement a simple screening questionnaire to detect patients at risk for depression (28) or other mood disorders which are often not adequate treated in patients with epilepsy (92). Screening tools should not replace an detailed evaluation, but can be an easy method to get fast information (92).

Especially earlier age at seizure onset and psychiatric comorbidities worsen the long-term prognosis for the patient significantly (43,46,48).

5.7 SOCIAL PROBLEMS

The diagnosis of epilepsy in childhood can have severe long-term consequences on the future life of the patients with sometimes significant social problems in adulthood (28). The illness identity is a strong predictor for the health related quality of life (96). Unfortunately, few studies exist which investigate social cognition and associated life quality (114).

Despite many people with juvenile myoclonic epilepsy declare in the long-term follow up study of C. and P. Camfield a good life quality and satisfaction regarding their social life and

health, a majority of the patients has at least one negative social outcome in their lives. The researchers conclude that: “Depression, social isolation, unemployment, and social impulsiveness complicate the lives of many patients” (45). In other studies, the long-term outcome was favorable, with a low rate of unemployment (108). In contrast to this, the social outcome of patients with Dravet syndrome is poor (15).

There is a strong multifactorial influence from the epilepsy observable on the social and educational outcome which also influences the economic situation and relationships of the patient in adulthood, as well as the independence of the patient (101). Patients with childhood-onset epilepsy with have lower grade-point averages, lower incomes and are more often unemployed (73). This is usually not caused by the education level of the parents of the patient, but directly due to the disorder (115). In general, the long-term social outcome of adults with epilepsy since childhood can be considered as poor. They have a higher risk for social isolation, a higher risk for unplanned pregnancy (59) and more problems with stable relationships (65). People with childhood-onset epilepsy, diagnosed between age 0-20 years, are less likely married, live more often alone and have a higher divorce chance (116).

Sometimes the social impairment can be even be comparable with people living in homeless conditions (28,101). Especially patients with genetic generalized epileptic seizures experience a negative social situation whereby the form of genetic generalized syndrome plays a subordinate role but the severity of disorder, respectively the effectiveness of seizure control, is an important factor (117) and seizure severity seems to be associated with social problems (118).

Furthermore, one aspect for the poor social outcome is the frequent decreased social cognition of the patients which is not easily detected during examination (101) and is related to neurological disabilities, polytherapy and drug resistant seizures. Intelligence and education level is after seizure control the second most important factor for psychosocial outcome (117).

One other burden of adults with childhood-onset genetic epilepsy is stigmatization.

Gabriel et al. observed that almost one-third of the participations felt stigmatized (101). The experience of stigmatization decreases the life quality of the patients (101). Sometimes patients are even more impaired through stigmatization than through their seizures and have problems to achieve their professional goals (58). Besides this, stigmatization can also have a negative effect on drug compliance (74). Education of the population about epilepsy and stigmatization could improve the situation for the patients (101).

In addition to this sexual and reproductive healthcare is often not practiced following the guidelines and there is sometimes a uncertainty of the health care provider regarding these topics (119). Because of the severity of many genetic epilepsies with childhood onset, the side effects of drug therapy and the negative long-term outcome, parenthood is not always possible. Due to the drug interactions, females with epilepsy have less choices of contraceptive options. If women get pregnant, they have poorer pregnancy outcomes and a higher risk for complications (100). Anxiety and depression in the peripartum period are much more common in women with epilepsy than without epilepsy (100).

Patients are often not able to live the way they want to live (78%), they feel that the epilepsy prevent them to do things other people can do (81%) and they also have lower expectations from the daily life (78%). The aspects which were most burdensome for the patients were independency, inability to drive, fear of brain damage, worsening of the condition, being a burden and seizures in public (79).Important prognostic factors for social long-term outcome of adults with childhood-onset genetic epilepsies are the severity of the seizures, seizure remission status and intellectual disability (59).

For best social outcome, efficient seizure control and a supportive environment is essential. Also, the identification of risk factors like chronic refractory epilepsy with high seizure frequency, poor family support, decreased cognitive performance and early intervention can improve the long-term outcome (117). To give the patient best support and increase the social outcome, the physician should be aware of signs for social impairment. It is possible to take social impairment as a special therapeutic target because there is evidence that social cognition deficits "make a unique contribution to impaired quality of life and social functioning" in patients suffering from epilepsy (114). Additionally, all involved therapists, also from other specialties, should empower and support the patient for best possible social outcome. Networking and synergy effects are beneficial in order to achieve this goal (101). Education and self-management interventions can increase the life quality and independence of the patient (120). Support for independency should be offered already to young people, to make for them the transition to adulthood easier and reach a better life quality (117).

6. DISCUSSION

The goal of this master thesis was, to find out which aspects are important and challenging for the treatment and care for patients with childhood-onset genetic epilepsies and which factors influence the positive long-term outcome of the patients.

A successful seizure control, good therapy adherence, a reduction of possible risks and side effects due to the ASMs and the treatment and care for social problems and psychological comorbidities improve the outcome for the patients. Furthermore, a good system of well-trained specialists and low barriers for health care are important goals to optimize medical care for these patients.

Unfortunately, there is not much data over long-term outcomes of adults with childhood-onset genetic epilepsy because the survival rates of the children were low in the past and not many people reached adulthood. Furthermore, genetic research is a relatively new field, many syndromes had – and still have – an unknown genetic etiology. This makes it more challenging to get specific data. More research and genetic testing in the future is necessary to get a bigger data basis of information to improve the treatment options of these patients and how do they differ the syndromes.

Regarding research, an important aspect is the problem of pharmacoresistant seizures, because persisting seizures are one of the most important reasons for decreased life quality and poor long-time outcome of the patients. Also, the burden and treatment of comorbidities have to be intensively evaluated, as well as positive factors which can improve the transition from children to adults. There is disagreement if quality of life and psychosocial long-term outcome is generally poor in patients with childhood-onset genetic epilepsy. The aspects leading to a positive psychosocial long-term outcome in the different syndromes and how they should be prioritized in the therapy should be further investigated.

7. CONCLUSION

In conclusion, adults with childhood-onset genetic epilepsy are complex and challenging patients, which need highly qualified support and care. These patients will need the care and treatment by adult neurologist more often in the future, since the life expectancy of patient with childhood-onset epilepsy has increased. Uncontrolled seizures are a risk factor for increased morbidity, mortality and decreased quality of life. Drug resistance is a frequent problem and leads to a worse long-term outcome. Also, polypharmacy should be avoided to reduce potentially unwanted drug side effects from ASMs. Negative side effects of ASMs can lead to reduced adherence, decrease life quality or are even harmful for the patient.

Also, the psychosocial long-term outcome is often poor. Comorbidities like depression, anxiety or isolation and stigmatization are frequent in adults with childhood-onset genetic epilepsy they can decrease quality of life of the patient enormously. As a consequence,

together with seizure control, these problems deserve particular attention of the treating physician. With regard to the psychosocial comorbidities, especially the transition phase from childhood to adulthood is a vulnerable time of the patient. Besides to effective seizure control, which is one of the most important treatment goals for patients with childhood-onset genetic epilepsy, treatment of psychosocial comorbidities is essential to increase the quality of life of the patient.

Furthermore, there is evidence that early onset of seizures is a negative prognostic factor for the long-term outcome of the patient. Early diagnosis in childhood, eventually reevaluation of the diagnosis in the adult patient and consequent treatment and care by a multidisciplined team due to seizure control and improved psychosocial outcome should be the goal for best results for the patient.

Unfortunately, currently there is often a care gap for the patients with childhood-onset genetic epilepsies due to a lack of knowledge of the adult neurologists regarding these syndromes. Especially the time of transition is a difficult time and challenging for patient and caretaker, but also a good chance to modify the treatment plan and reevaluate the diagnosis.

The challenges of the care for adults with childhood-onset genetic epilepsy are broad, hence to this, a multidisciplined therapy with additional specialists increases the positive outcome for the patient. Finally, a good treatment adherence is necessary to achieve best therapy success.

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