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Rhabdoid tumours of the central nervous system (AT/RT) – Brief information

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Table of Content

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1. General information on the disease

Rhabdoid tumours are rare, very aggressively growing tumours, which mostly occur in infants and toddlers during the first two years of life. They are „embryonal tumours“, which means that they originate from extremely immature (undifferentiated) cells. Rhabdoid tumours can develop in any tissue of the body. Most frequently, however, they affect brain and spinal cord (hence the central nervous system, CNS), the kidneys and the liver as well as soft tissues (such as in the neck, thigh or chestwall area).

Rhabdoid tumours of the central nervous system (CNS) are also known as “atypical teratoid rhabdoid tumours" – briefly AT/RT.

In about 50 % of cases, AT/RT develop in the so-called pontocerebellar angle in the area of the cerebellum from where they invade into adjacent structures. About 40 % of the tumours are found above the cerebellar tentorium (supratentorially), for example within the hemispheres. The remaining AT/RT distribute between the pineal gland (5 %), spinal cord (2 %) or occur at multiple sites (multifocal). Up to about 20 % of patients with AT/RT may present with metastases at diagnosis.

The following information is on rhabdoid tumours of the CNS only.

2. Incidence

Rhabdoid tumours are overall rare. Nevertheless, German experts assume that the incidence of these tumours has been estimated as too low until recently, since they haven’t been considered as a separate type of tumour and rather been assigned to other diseases instead. For example, a rhabdoid tumour of the central nervous system (AT/RT) was diagnosed as medulloblastoma based on its similar histological features. Current data of the European Registry for Rhabdoid Tumours (EU-RHAB) reveal that AT/RT in infants and toddlers appear as frequently as does medulloblastoma, which is the most common malignant brain tumour in children and adolescents. According to EU-RHAB, 15-22 patients per year have been newly diagnosed with AT/RT in Germany over the past years (please see chapter “Therapy optimising trials and registries” for more information on EU-RHAB).

AT/RT appear in almost all age groups, however, infants and toddlers in their first two years of life are most frequently affected (with about 80 %). The average age at diagnosis is about 1.5 years. Boys are slightly more affected than girls (gender ratio: 1.2:1).

3. Causes

The causes leading to the development of a rhabdoid tumour are not fully understood yet. A known fact, however, is that almost all (meaning over 95 % of) rhabdoid tumours – regardless of their localisation in the body – harbour alterations of a certain gene on chromosome 22. The affected gene is the *SMARCB1* gene (also known as *INI1*), which encodes the protein smarcB1. This protein plays a major role in controlling cellular mechanisms such as cell growth and differentiation. The genetic defect (mutation) leads to loss of protein function and subsequently to predisposition to malignant transformation and tumour development.

Most of the time, mutated SMARCB1 is only found in the tumour cells following spontaneous malignant transformation of a somatic cell. Less frequently (in up to 30 % of patients), the germline (germ cells) and thus all cells in the body are affected (germline mutation). Both a spontaneous genetic change in the patient's germline during embryonal development and (very rarely) a defect inherited from a parent are considered as causes. In both cases the disease is hereditary, meaning that the mutated gene and thus the predisposition to develop a rhabdoid tumour can be passed on to the offspring. Experts communicate this as "**R**habdoid **T**umour **P**redisposition **S**yndrome (RTPS). However, not all individuals harbouring a *SMARCB1* mutation will develop a rhabdoid tumour. Aside from *SMARCB1* mutations, *SMARCA4* mutations very rarely cause the tumour disease as well.

Good to know: In case of rhabdoid tumour predisposition syndrome, thus a germline mutation, the patient's siblings are also at an increased risk of developing the disease. Therefore, genetic councelling for the patient's whole family is recommended when a rhabdoid tumour is suspected (*see chapter "Diagnosis"*).

4. Symptoms

Due to the uncontrolled and aggressive growth pattern of rhabdoid tumours, symptoms typically develop and deteriorate within a few weeks. The presenting symptoms of these rhaboid tumours (AT/RT) (like other tumours of the central nervous system) primarily depend on the patient's age, the site and size of the tumour as well as its pattern of spread within the central nervous system (CNS). The following general (nonspecific) and local (specific) symptoms can occur:

4.1. General (nonspecific) symptoms

Unspecific general symptoms occur independently of the tumour's location. They may be similar to and therefore mimic other, non-CNS diseases. Infants and toddlers, as the most frequently affected age-group, typically present with shrill cries, irritability, fatigue, lethargy, loss of appetite, vomiting, developmental delay and/or failure to thrive. Wry neck (torticollis) as a result of cranial nerve impairment is also a common symptom. Older kids may complain about headaches and/or back pain as well as dizziness. General symptoms of a child or adolescent with a CNS tumour may also include increasing fatigue, inability to concentrate, school problems, mood swings, and character changes.

Major reason for these symptoms is the slowly but continuously increasing intracranial pressure (ICP). Elevated ICP may be caused by the growing, thus more and more space-occupying tumour

within the bony skull, but also by the tumour blocking the regular flow of the cerebrospinal fluid, thereby forming hydrocephalus. In babies or small children with soft spots (open fontanelles), elevated intracranial pressure and hydrocephalus typically present with a bulging fontanelle or a larger than expected head circumference (macrocephalus), respectively.

4.2. Local (specific) symptoms

Local symptoms may indicate the tumour location and, thus, which functional regions of the CNS may be affected. Therefore, a rhabdoid tumour in the cerebellum can cause impaired movement, visual deficits, dizziness and gait disturbances, whereas such a tumour in the hemispheres can be associated with motor and sensory deficits, seizures, speech disorders and behavioural problems, to name a few. A tumour in in the spinal cord area may cause serious back pain as well as palsies of various types (such as bladder and bowel incontinence).

Good to know: Not all patients presenting with one or more of the symptoms mentioned above do have a rhabdoid tumour or another type of brain tumour. Many of these symptoms may also occur with other, harmless diseases that are not associated with a brain tumour at all. However, if certain symptoms persist or get worse (for example repetitive headaches or rapid increase of head circumference in a young child), a doctor should be seen to find the underlying reason. In case it is a rhabdoid tumour or some other brain tumour, treatment should be started as soon as possible.

5. Diagnosis

If the paediatrician thinks that the young patient's history and physical exam are suspicious of a tumour of the central nervous system (CNS), the child should immediately be referred to a hospital with a childhood cancer program (paediatric oncology unit), where further diagnostics can be initiated and performed by childhood cancer professionals. Very close collaboration between various specialists (such as paediatric oncologists, paediatric neurosurgeons, paediatric radiologists, to name a few) is required, both to find out, whether the patient really suffers from a malignant CNS tumour and, if so, to determine the tumour type and the extension of the disease. Knowing these details is absolutely essential for optimal treatment and prognosis.

5.1. Imaging tests to confirm tumour existence

The initial diagnostic procedures for a young patient presenting with a suspected CNS tumour at a childhood cancer centre include another assessment of the patient's history, a thorough physical/ neurological exam and imaging diagnostic, such as sonography and magnetic resonance imaging (MRI). Rapid clarification may require computed tomography (emergency CT). These tests help to find out exactly whether the patient has a tumour of the central nervous system. Also, localisation and extent of the tumor as well as its demarcation regarding adjacent tissue can be diagnosed by these imaging techniques very well.

5.2. Tissue extraction (biopsy) to secure diagnosis

Final diagnosis of a CNS tumour requieres the removal of tumour tissue (biopsy). This usually requires surgery. The obtained tissue will be analysed under the microscope (histologically) as well as with immunohistochemical and molecular genetic methods. In particular, proof of *SMARCB1* mutation facilitates establishing the diagnosis of a rhabdoid tumour (*see chapter "Causes"*). In the context of immunohistochemical analysis, loss of the smarcB1 protein as a result of the mutation can be determined by specific staining of the tumour cells. Cytogenetic and molecular genetic testing provides direct proof of the genetic defect.

Once a *SMARCB1* mutation has been confirmed for the tumour tissue, blood cells will be tested for the mutation as well in order to rule out a germline mutation and rhabdoid tumour predisposition syndrome (RTPS), as in case of a germline mutation, the blood cells do contain the mutation as well. The germline mutation is particularly suspected in children under two years of age, in patients with tumours at multiple sites (synchrone tumours) or in case of a family history of tumour diseases, respectively.

In case a family history of rhabdoid tumour predisposition syndrome is known prior to biopsy, testing only the patient's blood for mutation is often sufficient to confirm diagnosis, since a malignant tumour revealed by diagnostic imaging and with *SMARCB1* mutation in the patient's blood cells is most likely an AT/RT.

5.3. Tests to assess spread of disease

Once the diagnosis of a rhabdoid tumour has been confirmed, additional tests are required to assess the extent of the disease within body. Since rhabdoid tumours are known to metastasize frequently and also may be found at multiple sites already at diagnosis – for example in the CNS and simultaneously in the kidneys – the initial finding of a single tumour is always followed by diagnostic imaging of the whole body. Apart from MRI scans of the complete CNS (brain and spine) as well as a total body scan for macroscopic metastases, these tests also include microscopic checking of the cerebrospinal fluid (CSF) for tumour cells in the spinal cord (which are not visible by MRI scan). Cerebrospinal fluid is mostly obtained from the spine in the lower back (lumbar puncture), since the risk of the puncture needle damaging the spinal cord is lowest at the lower back level.

5.4. Tests before treatment begins

In preparation for the intensive treatment of the brain tumour, further investigations are performed, such as electrocardiography (ECG) and/or echocardiography to check cardio function or electroencephalography (EEG) to test brain function. Furthermore, blood tests are needed to assess the patient's general health condition and to check whether the function of certain organs (such as liver and kidneys) is affected by the disease and whether there are any metabolic disorders to be considered prior or during therapy. Any changes occurring during the course of treatment can be assessed and managed better based on the results of those initial tests, which thus help to keep the risk of certain treatment-related side effects as low as possible.

5.5. Recommendations if a rhabdoid tumour predisposition syndrome is suspected

If a patient is diagnosed with a *SMARCB1* germline mutation – and, subsequently, at an increased risk for developing a rhabdoid tumour (rhabdoid tumour predisposition syndrome) –, one possible reason may be that the disease has been inherited by one parent. In most of the cases, however, it is more likely that the genetic defect is a result of a new mutation. If inheritance is the case, both the patient's parents and siblings are at a higher risk to develop a rhabdoid tumour as well. In order to rule out this risk or to diagnose it as early as possible, certain blood tests will be recommended. If those come back positive for a germline mutation in one of the parents, the patient's siblings should also be tested. These tests are usually done in human genetics laboratories. Also, genetic councelling is recommended.

6. Treatment planning

After the diagnosis has been confirmed, therapy is planned. In order to design a highly individual, risk-adapted treatment regimen for the patient, certain individual factors influencing the patient's prognosis (called risk factors or prognostic factors) are being considered during treatment planning (risk-adapted treatment strategy).

One important prognostic factor is the patient‘s age at diagnosis: it determines treatment intensity and, therefore, has an impact on the patient's chances of survival. For example, radiotherapy – a very efficient treatment method for rhabdoid tumours – is only a limited option for children under the age of three and no option at all for children under the age of 18 months. Also, the tolerance of this treatment is significantly reduced in very young children when compared to other methods (such as surgery, chemotherapy).

Further prognostic factors are the type (hereditary or non-hereditary), the localization, size and spread of the tumour. Hereditary disease (germline mutation), for example, is known as an unfavourable prognostic factor and so is metastasis at the timepoint of tumour diagnosis. Both scenarios are associated with a lower probability of eliminating all tumour manifestations (which is known to promote favourable prognosis). Response of the disease to chemotherapy is also a prognostic factor.

All these factors are included in treatment planning in order to achieve the best outcome possible for each patient.

7. Treatment

Treatment of children and adolescents with rhabdoid tumour should take place in a children's hospital with a paediatric oncology program. Only such a childhood cancer centre provides highly experienced and qualified staff (doctors, nurses and many more), since they are specialised and focussed on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts. The doctors in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised.

The goal of the treatment is to achieve high cure rates while avoiding side effects as much as possible. Considering the usually very young age of patients with a rhabdoid tumour, this is a huge challenge. Infants and toddlers are highly vulnerable; they suffer severely of acute side effects and long-term sequelae of the aggressive therapy and are therefore hard to treat. Hence, the most important step prior to or during therapy is to decide whether treatment should be initiated or continued, respectively, and if so, whether the goal is cure (curative approach) or managing symptoms (palliative approach).

Since 2007, patients with rhabdoid tumour have received treatment according to a standardized therapy protocol under the roof of the EU-RHAB Registry (so-called consensus treatment strategy, *see chapter „Therapy optimising trials and registries“*). The following information on therapy is based on the recommendations of the EU-RHAB Registry.

7.1. Treatment methods

Treatment options for patients with rhabdoid tumour include surgery, chemotherapy and radiotherapy. For some patients, high-dose chemotherapy followed by autologous stem cell transplantion may be an option, too. The individual treatment choice is based on the patient's age and general health status as well as on the tumour type and its extent at diagnosis and after surgery.

Neurosurgery and radiotherapy are of highest impact in the treatment of patients with rhabdoid tumour. Yet, surgery or radiation cannot be performed in every child. Chemotherapy (and, for some patients, high-dose chemotherapy) can help improve prognosis and – particularly in very young children – delay or even completely avoid radiotherapy.

7.1.1. Surgery

First step when treating a patient with rhabdoid tumour is maximal neurosurgical tumour removal, if possible, since the extent of tumour resection has a major impact on the subsequent course of the disease. The more radically the tumour can be resected, the higher are the chances of long-term survival. If the tumour is localized and has not spread, second look surgery to achieve gross total removal is an option. Unfortunately though, complete resection is impossible in most cases (in about 70 % of patients) without also removing healthy tissue and without jeopardizing the patient's quality of life. This is related to the frequently unfavourable tumour location, the patient's young age as well as the frequent presence of metastases at the timepoint of tumour diagnosis.

Aside from tumour removal, neurosurgery also includes the implantation of a catheter into one of the brain's ventricles for subsequent chemotherapy. The catheter is connected to a small, dome-shaped, soft plastic device (Ommaya reservoir or Rickham reservoir) placed under the patient's scalp, through which chemotherapy can directly be delivered into the cerebrovascular fluid (*see next chapter*).

7.1.2. Chemotherapy

Surgery is followed by intensive chemotherapy in order to improve the patient's chances of cure. Chemotherapy uses drugs (so-called cytostatic agents) that can kill fast-dividing cells,

such as cancer cells, or inhibit their growth, respectively. In order to optimize treatment efficacy, combinations of different agents are given in different treatment blocks.

Standard therapy according to the EU-RHAB recommendation includes up to 12 treatment blocks. These include the agents doxorubicine (DOX) and combinations of ifosfamide, carboplatin and etoposide (briefly: ICE) or vincristine, cyclophosphamide and actinomycin D (briefly: VCA), respectively, which are given intravenously in alternation. By the intravenous route, they get distributed in the blood system and can, thus, eliminate tumour cells throughout the whole body (systemic chemotherapy). In addition to this ap-proach, some chemotherapy (methotrexate, MTX) is given directly into the cerebrovascular fluid, which surrounds both brain and spinal cord (intrathecal or intraventricular chemotherapy). This is necessary, because most chemotherapeutic agents cannot pass the barrier between blood and brain.

7.1.3. High-dose chemotherapy and autologous stem cell transplantation

For some patients, high-dose chemotherapy followed by autologous stem cell transplantation may be an option instead of the conventional chemotherapy described above. In this case, the patient receives treatment with carboplatin and thiotepa (CARBO/TT) after six cycles of standard chemotherapy. The chemotherapy doses of this regimen are considered high enough to also eliminate otherwise treatment-resistant tumour cells in the body.

Since the high doses of cytostatics given according to this treatment strategy also lead to the destruction of the blood-forming cells in the bone marrow, the patient will receive blood-forming stem cells in a second step. These stem cells are obtained from the patient's blood or bone marrow prior to high-dose chemotherapy and are given back right after this treatment (so-called autologous stem cell transplantation, SCT). Precondition for carrying out this treatment is, however, that most of the tumour load has been destroyed by the preceeding standard regimen, thereby having achieved a so-called remission. Also, the patient's age and clinical condition are of relevance.

It is still unclear so far whether the high-dose regimen provides a prognostic benefit over the conventional chemo- and radiotherapy. This question is currently being addressed by a recently activated European study (UMBRELLA-Study SIOPE ATRT01).

7.1.4. Radiotherapy

Depending on the patient's age, radiotherapy may be recommended during or after chemotherapy. Radiotherapy is carried out using energy-rich, electromagnetic radiation, given through the skin to the tumour region. Radiation causes DNA damage in tumour cells, thereby leading to cell death.

Aside from complete surgical tumour removal, radiotherapy is one of the most important measures for treatment of a rhabdoid tumour. However, its application is limited due to treatment-induced late effects. This particularly affects infants and toddlers, whose brains are still developing: it is well-known, that radiation early in life results in serious impairment of normal cognitive development. Therefore, chemotherapy and, if applicable, even high-dose chemotherapy are used to delay radiotherapy as long as possible.

If radiotherapy is an option, timing, volume and type (photons versus protons) are determined based on the patient's age, the vulnerability of the tissue and prognostic factors. According to the treatment recommendations of the EU-RHAB Registry, radiotherapy is considered for children 12-18 months of age with localized disease. These patients will receive a total dose of 54 Gray (Gy) to the tumour region. For children whose tumour has spread within the central nervous system via the cerebrovascular fluid (leptomeningeally metastasized tumours), radiation of the brain and spinal cord (craniospinal radiotherapy) are considered once they are three years old. Fore these patients, a dose of 35.2 Gy to the whole central nervous system plus an additional dose (boost) to the tumour site (up to a total dose of 55 Gy) are recommended.

Modern radiation techniques, such as Intensity-Modulated Radiotherapy (IMRT) help minimise the damage of healthy tissue. For some patients, radiotherapy with protons instead of conventional radiotherapy (with photons) may be an option, for example for very young children or in case proton therapy is expected to have a clear advantage compared to conventional radiotherapy. This type of radiotherapy provides the benefits of better targeting the tumour area, thus sparing more adjacent, healthy tissue from the effects of radiation. Proton therapy is gaining an increasing importance in the treatment of children and teenagers with solid tumour.

7.1.5. New treatment approaches

Despite oft he currently available intensive treatment modalities, cure rates for children with AT/RT are unsatisfying. This particularly applies to high-risk patients (metastasised tumour and/or very young age at diagnosis). In addition, the intensive treatment does not only cause acute side effects, but also long-term sequelae (such as endocrinological deficits, which are associated with certain developmental delays, or impairments in hearing or vision). This may seriously impair the patients' quality of life.

Scientists keep studying these tumours intensely to find new agents and treat-ment modalities. The current research focuses on the molecular mechanisms leading to the developments and growth of rhabdoid tumours. The analysis of cellular signalling pathways that are altered in rhabdoid tumours have helped identifying different agents, which may be of benefit in the treatment of rhabdoid tumours. Promising new treatment strategies will be examined in the framework of clinical studies.

For patients with a relapse of an AT/RT, various approaches apply to individual treatment attempts. These include epigenetically active agents like decitabine on the one hand, but also the drug ribociclib and so-called checkpoint inhibitors. The researchers at the EU-RHAB Registry are working hard to find new drugs and get them approved for clinical use. This should always be carried out as clinical studies (*see also next chapters*).

8. Therapy optimising trials and registries

In the large paediatric treatment centres, children and teenagers with rhabdoid tumour receive therapy according to standardized treatment plans (protocols). These protocols are designed by experts with the goal to improve the patient's prognosis and are usually applied within therapy optimizing trials or registries.

Therapy optimising trials are standardised and controlled clinical trials that aim at steadily developing and improving treatment concepts for sick patients based on the current scientific knowledge. Patients who cannot participate in any study, for example because none is available or open for them at that time, or since they do not meet the required inclusion criteria, respectively, are often included in a so-called registry. Such a registry primarily serves to acquire all clinical, molecular genetic and treatment-associated patient data in ordert o gain a better understanding oft he tumour biology. Furthermore, the registry center supports the doctors at site with (non-commital) treatment recommendations based on the most recent data on best treatment options, in order to provide the patient with optimal therapy even without the framework of a clinical study.

Current trials and registries

Since rhabdoid tumours are very rare, experts of the Society of Paediatric Oncology and Haematology (GPOH) initiated during a consensus conference in Italy in 2007 that all patients with rhabdoid tumours in a part of Europe should be registered with the European Rhabdoid Registry (**EU-RHAB Registry**) and treated according to a standardized strategy (consensus strategy). The treatment regimen was designed by an international competence network and is outlined in the chapter “Treatment”. It has been validated for all rhabdoid tumours (regardless of their localisation in the body) and requires adjustment to the individual patient.

22 countries are currently registering their patients with this EU-RHAB Registry. Treatment centres in Germany, where children and adolescents with cancer are being treated, are legally obliged to register their patients with the appropriate studies or registries. The decision on whether treatment will be according to the registry’s recommendations is made locally by the individual treatment group. As parents, you are encouraged, however, to ask for treatment for your child according to the EU-RHAB recommendations. The European Registry headquarters are located at the University Hospital in Augsburg, Germany, and the principal investigator is Prof. Dr. Dr. med. Michael C. Frühwald.

Good to know: in July 2021, an international, multicentric UMBRELLA trial has been opened for children with AT/RT: the **SiOPE ATRT01 trial**. In the framework of this multipart study, patients are being assigned to one of three therapy arms (part A: 12-35 months, part B: under 12 months, part C: older than 35 months) based on their individual risk profile (in particular age at diagnosis). **There will be more information on this study soon.**

9. Prognosis

Though the chances of cure (prognosis) for children with newly diagnosed rhabdoid tumour have significantly improved thanks to intensive treatment concepts within the framework of EU-RHAB, they are still unfavourable. The average overall 5-year-survival rate is 35 to 50 %. However, in individual patients, prognosis is dependent on various factors, such as the patient’s age at diagnosis, tumour type (hereditary or non-hereditary) as well as tumour size, site and extent and, thus, possibility of complete tumour removal.

Patients with localized, non-metastasized, surgically removable and non-hereditary rhabdoid tumour, who are older than three years of age at diagnosis, usually have favourable probabilities of cure, given that the tumour can be completely removed and early radiotherapy is possible.Children between their first and third birthday with the same co-factors have a comparably higher risk of relapse and thus less favourable outcomes. Prognosis is particularly unfavourable for infants and toddlers under one year of age. The same applies to all other patients with unfavourable prognostic factors such as a high-risk rhabdoid tumour. These include patients with germline mutation, and thus a predisposition for the development of rhabdoid tumour, as well as patients with surgically unremovable primary tumour or metastasized disease, respectively. However, patients who do benefit from treatment (surgery, chemotherapy, in some cases high-dose chemotherapy and radiotherapy) despite of unfavourable prognostic factors, so that long-term survival may be possible.

New molecular treatment approaches are currently being analysed in the framework of therapy optimising trials. The goal is to optimize cure rates also for high-risk patients.

Note: The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with this kind of brain tumours. They do not predict individual outcomes.

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