GUIDELINES

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Polish recommendations for diagnosis and therapy of paediatric stroke

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ABSTRACT

Stroke remains one of the greatest health challenges worldwide, due to a high mortality rate and, despite great progress in its treatment, the significant disability that it causes. Studies conducted around the world show that the diagnosis of stroke in children is often significantly delayed.

Paediatric ischaemic arterial stroke (PAIS) is not only a problem that varies greatly in frequency compared to the adult population, it is also completely different in terms of its risk factors, clinical course and outcome.

The main reason for the lack of a rapid diagnosis of PAIS is a lack of access to neuroimaging under general anaesthesia. The insufficient knowledge regarding PAIS in society as a whole is also of great importance. Parents and carers of children should always bear in mind that paediatric age is not a factor that excludes a diagnosis of stroke.

The aim of this article was to develop recommendations for the management of children with acute neurological symptoms suspected of ischaemic stroke and further treatment after confirmation of the ischaemic aetiology of the problem. These recommendations are based on current global recommendations for the management of children with stroke, but our goal was also to match them as closely as possible to the needs and technical diagnostic and therapeutic possibilities encountered in Poland. Due to the multifactorial problem of stroke in children, not only paediatric neurologists but also a neurologist, a paediatric cardiologist, a paediatric haematologist and a radiologist took part in the preparation of these recommendations.

Key words: stroke, paediatric, risk factors, diagnosis, treatment

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Introduction

Stroke remains the third most common cause of death worldwide, after cardiovascular disease and cancer, despite tremendous progress in its treatment. Around the world, about 17 million people suffer a stroke each year, and about 90,000 of these are registered in Poland.

Paediatric arterial ischaemic stroke (PAIS) is not only a problem that is significantly different in its incidence compared to the adult population, but it has also completely

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different risk factors and prognosis. The PAIS incidence rate is estimated at c.3–13 new cases per 100,000 children per year. This frequency range is due to several reasons, i.e. the ages of patients recruited for the studies (including newborns or an extension of recruitment up to 21 years of age), the recruitment of children with any type of cerebral vascular disease including haemorrhagic stroke or cerebral venous thrombosis of the brain (CVT), and another factor that leads to differing incidences is geography, e.g. in the basin of the Mediterranean Sea and in sub-Saharan Africa, children with sickle cell disease (SCD) will be more often affected [1, 2].

Therefore, for practical and methodological reasons, it is necessary to define PAIS and the correct use of this term for confirmed cases.

PAIS is an acute neurological deficit of sudden onset in children aged between 29 days and 18 years, and the results of neuroimaging tests show acute ischaemic changes corresponding to the range of symptoms observed in the patient [3–5].

Late diagnosis of stroke in children is a worldwide problem, especially when contrasted with the diagnosis of adult patients. Frequently, the delay in making a correct diagnosis after the onset of symptoms of stroke can take several days. This means that the child is excluded from thrombolytic treatment, because the therapeutic window remains the same for children and adults.

The crucial reason for the delay in PAIS diagnosis is lack of access to neuroimaging under general anaesthesia. Moreover, in children with acute neurological symptoms, a large proportion of changes detected in radiological studies are pathologies different from ischaemic stroke (so-called 'stroke mimics') [6].

A lack of understanding in society in general, and among parents and caregivers in particular, about the fact that paediatric age does not exclude stroke is also very important. The consideration of stroke in differential diagnosis is likewise inadequate among medical staff and doctors. This means that training programmes for radiologists, as well as for paediatricians and paediatric neurologists, are necessary to improve the accuracy and promptness of PAIS diagnoses.

Bearing in mind the specificity of childhood stroke, special attention should be paid to risk factors for its occurrence in children. The most common are arteriopathies with pathologies of the arterial wall being a cause of acute cerebral ischaemia. Among arteriopathies, the most prevalent is so-called focal cerebral arteriopathy of childhood (FCA), affecting large arterial vessels such as the middle cerebral artery (MCA) with uni- or bilateral location. Upper respiratory tract infections are a predisposing factor for FCA, and its nature is often reversible. Dissection of extracerebral arteries in children and adolescents, usually due to trauma, accounts for c.20% of the arteriopathies associated with stroke in children.

The recommended diagnostic method in the case of suspected PAIS is magnetic resonance imaging. If however this technique is not available, then a computed tomography examination is acceptable [2, 7, 8]. The frequency and variable localisation of vascular lesions in PAIS contribute in turn to the scope of imaging diagnostics in a child with suspected ischaemic stroke. The current recommendations for the diagnostics of a child with sudden symptoms of central nervous system impairment indicate the need for head and neck imaging, taking into account angio mode. Otherwise, if cervical vessels and structures are not assessed in radiological scans, an important arteriopathy such as extracerebral dissection might be overlooked and not properly treated [2, 7, 8].

The current classification of paediatric stroke, CASCADE (Childhood AIS Standardised Classification and Diagnostic Evaluation), which includes seven categories, also places strokes in the course of various arteriopathies in items 1–4; indicating at the same time a possible variety of their aetiologies (i.e. genetic, metabolic, or infectious) and their course (stable, progressive, or reversible). A follow-up neuroimaging examination is required to determine the extent of the course of arteriopathy, and the recommended period is 3–6 months after disease onset. Category 5 in the CASCADE classification is a cardiac-embolic stroke, which in turn affects the youngest children with congenital heart defects, often requiring numerous surgeries.

Nearly 40% of all childhood strokes occur under the age of five years. This fact contradicts the popular belief that there is no stroke in children. Moreover, newborns are a group in which stroke occurs much more often than does AIS in children over 29 days of age; but due to specific risk factors and the course of neonatal stroke, this is excluded from the PAIS category [9].

Idiopathic aetiology of childhood stroke is another element that significantly distinguishes it from stroke in adults, when despite extensive laboratory and imaging diagnostics, none of the well known risk factors for acute cerebral ischaemia can be found.

Today, in the adult population with stroke, thrombolytic therapy is common, provided that a stroke is diagnosed and that contraindications have been ruled out within the therapeutic window, i.e. 4.5 hours from the onset of clinical symptoms. Australian and American recommendations indicate the possibility of using intravenous thrombolysis under these conditions in children aged 2–17 years. According to the Summary of Product Characteristics in Poland, this treatment can be considered in children aged 16 years or older. In turn, endovascular therapy can be performed in children with a stroke up to six hours after its onset. Uncertainty about the timing of a stroke is a contraindication to both of the above procedures.

For all children with PAIS, initial therapy with unfractionated heparin, low-molecular heparin or aspirin is recommended until a cardioembolism or a dissection has been excluded. Aspirin for another two years is recommended even after the exclusion of the two reasons mentioned; for cardioembolic aetiology or vascular dissection, low-molecular weight heparin

(LMWH) or vitamin K antagonists would be appropriate for 6–12 weeks after stroke onset [7].

The purpose of this paper was to develop recommendations on how to deal with a child with acute neurological symptoms being suspected of an ischaemic stroke, and for further treatment after confirming the ischaemic aetiology of the problem. These recommendations are based on the current global recommendations for the management of children with stroke, but our goal was also to match them as closely as possible to the needs and technical diagnostic and therapeutic possibilities encountered in Poland.

Obviously, although paediatric stroke, as has been repeatedly emphasised, is not a 'tracer' of adult stroke, the experience of 'adult' neurologists dealing with stroke contributes to the management of children. For this reason, the team developing our recommendations included 'adult' neurologists. On the other hand, due to the multifactorial and complex basis of stroke in children, the team also included a cardiologist, a haematologist and a radiologist because our goal was to not only set out theoretical assumptions, but above all to convey the experience and practical knowledge of a group of people experienced in dealing with paediatric stroke.

When preparing the guidelines, we used the tips contained in the work by Graham ID, Harrison MB, Brouwers M et al., 2002 [10].

Paediatric stroke recommendations — definitions, epidemiology and clinical presentation in acute phase

For a diagnosis of paediatric ischaemic stroke, several conditions must be met:

1. occurrence of a sudden neurological deficit with an acute onset;
2. results of radiological examinations, i.e. magnetic resonance imaging (MRI) or computed tomography (CT), showing the presence of a stroke/strokes of vascular origin and corresponding to known ranges of arterial vascularisation as well as clinical symptoms;
3. symptoms occurring in a child aged between 29 days and 18 years [11–14].

According to various researchers, the prevalence of ischaemic stroke in children is estimated at between 1.2 and 7.9 per 100,000 child population per year [15–16].

These differences in the estimated prevalence of AIS in children result from several factors, such as the age of the patients recruited for the study (e.g. just the neonatal period, or with an upper age limit ranging between 16 and 19 years), various ethnic origins, and thus various factors risk of AIS (e.g. moya moya disease and sickle cell disease), and whether or not to include patients with heart defects and patients diagnosed with TIA (transient ischaemic attack) or CVT.

Less than half of childhood strokes affect patients under 5 years of age, and it is largely determined by the number of cases of cerebral ischaemia in children with congenital heart defects. In the entire paediatric population, stroke occurs more often in boys than in girls; the neonatal population, especially preterm infants, is also characterised by a higher incidence of strokes due to risk factors specific to this age group [17–23].

Clinical symptoms of a child's stroke depend on three factors: the patient's age, and the location and the size of the brain ischaemia. In newborns and young infants, the symptoms of stroke are disturbances of consciousness and epileptic seizures, including so-called 'subtle seizures'.

Neurological symptoms associated with the occurrence of stroke in adult patients, can also concern older children. In the case of localisation of an ischaemic focus in the anterior circle of cerebral circulation (i.e. arteries: ICA, the Internal Carotid Artery, MCA, the Middle Cerebral Artery, and ACA, the Anterior Carotid Artery), the symptoms of a stroke will be paresis or hemiplegia, central paresis of the facial nerve on the side of limb paresis, semi-amblyopia, and aphasia (speech disorder) which may be motor, sensory or mixed, in the case of dominant hemisphere involvement. In some patients, these symptoms are accompanied by, or preceded by, symptoms such as headache, nausea, vomiting and/or convulsions, which are an expression of increased intracranial pressure syndrome.

On the other hand, if the stroke is located within the posterior part of the cerebral vascularisation, the clinical picture will be dominated by the features of the cerebellar syndrome.

In the paediatric population, anterior strokes occur much more frequently than those in the posterior part of brain circulation. The division of strokes into PACI (Partial Anterior Circulation Infarct), TACI (Total Anterior Circulation Infarct), LACI (Lacunar Infarct) and POCI (Posterior Circulation Infarct) was based on the location of vascular changes in stroke patients, and it concerns both adults and children with stroke [24–27].

The most important risk factors for death in the early phase of childhood stroke are the patient's young age, the presence of a heart defect, and the large size of the stroke [26]. Malignant middle cerebral artery syndrome is characterised by a dramatic course, with rapidly increasing cerebral oedema and deterioration of the patient's condition; in patients not qualified for decompressive craniectomy, the course of the stroke is usually fatal.

Paediatric stroke recommendations — risk factors

The factors predisposing towards paediatric arterial ischaemic stroke (PAIS) are numerous, and it is not uncommon for one patient to recognise several comorbid factors. Such coincidences make the ischaemia more likely to recur (see Table 1).

The first group of factors, cerebral arteriopathies, are any pathologies of the cerebral vessel wall, both congenital and acquired, of a transient, stable or progressive nature, which cause abnormal cerebral flow and, consequently, cerebral

Table 1. Risk factors of paediatric arterial ischaemic stroke (PAIS)

Cerebral arteriopathies	
FCA (focal cerebral arteriopathy of childhood)	
Moya moya disease and syndrome (e.g. in course of SCA, sickle cell anaemia)	
Vascular wall dissection	
PVA (post-varicella arteriopathy)	
Congenital blood wall defects, e.g. hypoplasia, fibro-muscular dysplasia	
Congenital and acquired heart diseases/defects	
Thrombophilia (prothrombotic state)	**Congenital**
	High lipoprotein(a)(lp(a) serum concentration
	Protein C (PC) deficiency
	Protein S (PS) deficiency
	Antithrombin III (ATIII) deficiency
	Activated protein C resistance (APCR)
	Genetic polymorphisms of genes of coagulation factors
	Factor V G1691A
	Factor II G20210A
	MTHFR C667T
	Factor XIII Val34Leu
	Fibrinogen A (FGA) Thr312Ala
	Fibrinogen B (FGB) G455A
	Acquired
	Antiphospholipid syndrome (APS)
URI (upper-respiratory infection), generalised infection (sepsis)	
Connective tissue diseases	
Traumas	
Intoxications (e.g. amphetamines, cocaine)	

Table 2. Recommended tests for thrombophilia screening

*It is necessary to refer the results to the norms for different age groups [70–74, 77, 83–84].
**A single finding of deviations in the results requires control (except for pathogenic mutations).
— coagulation tests:
APTT, PT, fibrinogen; thrombin time (TT)
— antithrombin (AT)
— protein C
— free protein S
— activated protein C resistance (APCR) → in more than 95% corresponds to factor V Leiden mutation
— factor V Leiden mutation
— prothrombin G20210A mutation
— homocysteine → in the case of abnormal result, testing for MTHFR gene polymorphism
— lipoprotein (a)
— antiphospholipid antibodies: anticardiolipin antibodies (aCL), anti-β2-glycoprotein I antibodies (anti-β2GPI); lupus anticoagulant (LA); activity of clotting factors: VIII, IX, XI
***To be considered:
— plasminogen
— tissue plasminogen activator (t-PA)
— tissue plasminogen activator inhibitor 1 (PAI-1) → in the case of abnormal PAI-1 results, testing for 4G/5G polymorphism in the PAI-1 gene

ischaemia. The most common in this group is FCA, which affects large cerebral vessels (e.g. the ICA or MCA), unilaterally or bilaterally, and the nature of which is often reversible.

Of the acquired arteriopathies, vascular wall dissection, most often associated with neck trauma, deserves attention; this problem accounts for c.20% of arteriopathies associated with the risk of childhood stroke. Indeed, this possibility is the reason why imaging of the vessels of the head and neck to the aortic arch is included in the recommendations for the methodology of neuroimaging in children with suspected stroke [3, 11, 28–30].

The second group of risk factors of acute cerebral ischaemia in the paediatric population is congenital, and less frequently acquired, heart disease [33–35].

Another group of factors contributing to the occurrence of PAIS are coagulation disorders, congenital or acquired, known as thrombophilia or prothrombotic state [12,31].

In the differential diagnosis of stroke risk factors in the pediatric population, infections should also be taken into account, among which is the presence of post-varicella arteriopathy (PVA) as a consequence of chickenpox. Upper respiratory tract infections deserve special attention (URIs, upper respiratory infections) as they are considered a predisposing factor for FCA. Moreover, the possibility of intoxication with amphetamines or cocaine as a risk factor for PAIS has been included in the set of laboratory tests [12, 31].

Despite the described imaging methods and laboratory diagnostics, in as many as one third of children with ischaemic stroke, it is not possible to determine the aetiology.

Paediatric stroke recommendations — acute phase management

The scheme for dealing with a child with acute CNS (central nervous system) symptoms/suspected acute cerebrovascular disease, is based on the 2017 recommendations of the RCPCH, the Royal College of Paediatrics and Child Health, as well as on the guidelines developed in 2019 by a team of specialists from the AHA, the American Heart Association/ /American Stroke Association [35–36].

For a quick assessment of symptoms in a patient, including a child, the simple FAST (Face Arm Speech Time) mnemonic is useful:

F — face asymmetry (i.e. sudden onset of paresis of facial muscles);

A — arm drift (i.e. sudden upper limb weakness);

S — speech disturbances (i.e. sudden onset of aphasia or dysarthria);
T — time (summon ambulance as soon as possible and transport patient to hospital to qualify for treatment of causal stroke).

Correctly collected history is of great importance in the diagnosis of a stroke. When a stroke is suspected, the timing of the first symptoms, the circumstances of the onset of the disease, the possibility of trauma to the skull, throat or neck, upper respiratory tract infections, and drug poisoning are important facts to gather. The course of symptoms (sudden, relapsing), the sequence of neurological symptoms, and the circumstances of their occurrence are all important. When taking an interview, account should be taken of previous diseases, the presence of heart disease, medications used, unexplained fever (systemic diseases), and psychomotor retardation. Family history, the presence of hypertension, diabetes, atherosclerosis, and genetically determined diseases are also important.

In a suspected childhood stroke, i.e. a sudden neurological deficit in a patient aged 29 days to 18 years, or in the neonatal period a neonatal stroke, the child should immediately be sent to the accident and emergency department of a hospital prepared for the treatment of children with stroke. A multidisciplinary stroke team including a paediatric neurologist, a neuroradiologist/radiologist, and an anaesthetist, should be available 24/7. A paediatric cardiologist, a paediatric haematologist, a physiotherapist, and a neurosurgeon should also be available in the hospital treating a child with stroke.

On the way to the hospital, it is necessary to secure the intravenous catheter, to monitor blood pressure, heart rate and respiration — oxygen therapy (goal sat > 92%), and to control and symptomatically treat hypoglycaemia, fever and convulsions.

Laboratory tests to be performed on admission to the hospital/A&E department:

- Blood tests: blood gas analysis, complete blood count with smear, CRP (C-reactive protein), blood coagulation parameters, glucose level, electrolytes: sodium, potassium, calcium, magnesium, phosphorus; creatinine, urea, transaminases, bilirubin, urine.
  Vital functions should be monitored constantly.
  - Evaluation of child's condition using Glasgow Coma Scale and PedNIHSS score.
  - Enclosed is a workflow, Glasgow Scale and PedNIHSS.
  - Every child suspected of having an acute stroke should have an urgent neuroimaging examination after going to the hospital — recommended for children are MRI or CT and/or with vascular examination (MR/ /CT angiography) — up to one hour after the child is admitted to hospital [7]. Further treatment depends on the diagnosis.
- In case of ischaemic stroke: ASA (acetylosalicylic acid) or LMWH/UFH (unfractionated heparin) treatment to be considered. If conditions are met: thrombolysis, thrombectomy or decompressive craniectomy if necessary.
- Haemorrhagic stroke:
  - Urgent contact with a neurosurgeon is necessary — surgical treatment to be considered
  - ICU care (intensive care unit) — anaesthetist
- Stroke mimic: further management is based on clinical symptoms, and the result of an imaging examination; a careful history should be taken into account.

Paediatric stroke recommendations — imaging diagnosis

The logistics of admitting a child with a suspected stroke to the paediatric accident and emergency department should aim at performing neuroimaging tests as soon as possible. In a child with suspected stroke, imaging of the brain should be performed immediately, and preferably within 60 minutes of arrival at hospital. Magnetic resonance imaging (MRI) diagnostics is the method of choice in children with suspected stroke, in the absence of contraindications to its performance.

The final decision to perform a specific imaging test, i.e. computed tomography (CT) or MRI, should be made depending on the availability of these methods, and on the centre's own procedures and experience in neuroradiological diagnostics in children.

MRI has higher sensitivity and an undoubted advantage over CT in detecting ischaemic changes in the acute and hyperacute phases, and their differentiation from other sudden states imitating a stroke (bearing in mind that in children stroke-mimics are more frequent than in adults) [35–38].

In the detection of a haemorrhagic stroke, both CT and MRI techniques are similarly effective, but it is easier to recognise the presence of blood in the subarachnoid space in a CT. CT imaging of the brain should not be delayed if MRI, general anaesthesia or staff are not available. If it is impossible to perform a CT or MRI scan in a given unit, the child should be immediately transported to a centre equipped with full diagnostic capabilities [40–44].

These are the recommended neuroimaging diagnostic guidelines in the case of a child suspected of stroke:

1. Every child suspected of having an acute stroke should immediately undergo a neuroimaging diagnosis (no later than 60 minutes after arriving at the hospital) in order to confirm or rule out the diagnosis of ischaemic stroke. This is very important when deciding to start thrombolytic treatment.
2. Magnetic resonance imaging or computed tomography should be performed, depending on the availability of these techniques and on the centre's own experience in paediatric neuroradiological diagnostics. Whether or not to perform the examination under general anaesthesia, especially in young children who are agitated or who are unable to remain motionless throughout the examination

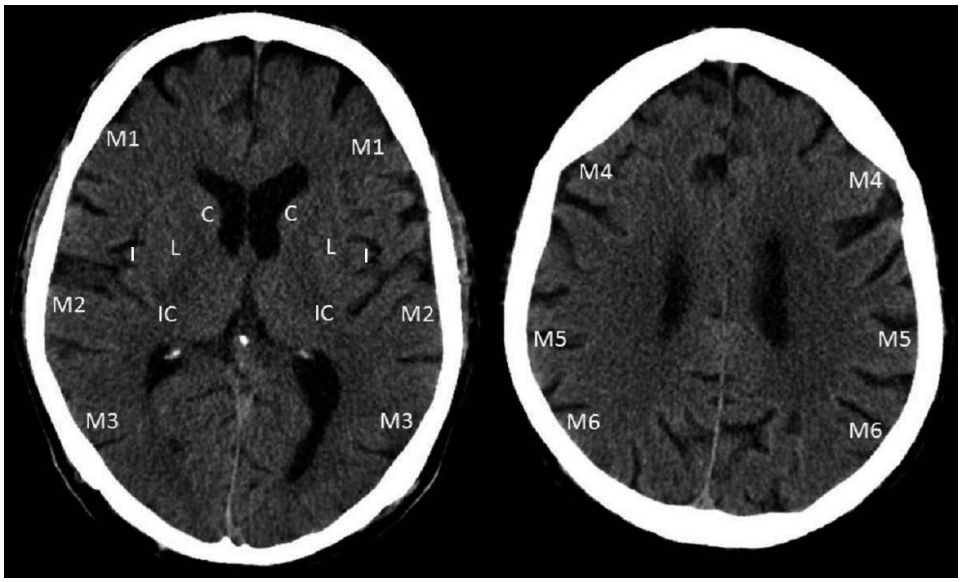

Figure 1. Extent of MCA vascularisation on both sides with marked areas, enabling assessment of ischaemic lesions on ASPECTS scale. Markings as follows: Alberta Stroke Programme Early CT Score (ASPECTS) — a scale used to quantify early ischaemic changes in CT, where C — caudate nucleus; L — lenticular nucleus; I — island; IC — inner capsule; M1 — anterior cortical area part frontal lobe; M2 — cortical area lateral to island ribbon; M3 — posterior cortical area temporal lobe; M4 — anterior area located above M1 area; M5 — central area located above M2 area; M6 — posterior area located above M3 area

period, should be taken into account (CT — 1–3 minutes, MRIc. 7–20 minutes). Some children who will require MRI anaesthesia will be able to have a CT scan without the need for anaesthesia.

3. Ischaemic stroke from onset until 7–10 days after acute symptoms can be diagnosed on the basis of DWI (diffusion-weighted imaging) sequence which is the most sensitive and specific tool for ischaemia detection in the first minutes.
4. MRI examination is the examination of choice in children suspected of having acute stroke.Due to the race against time, the MRI examination should be as short as possible.

The most important sequences are DWI, T2* or SWI (susceptibility-weighted imaging), FLAIR (fluid attenuated inversion recovery) and optionally T1 weighted images with TOF (time of flight) MRA (magnetic resonance angiography). The examination time must not exceed 15 minutes in the basic version without TOF MRA. It is recommended that this should be less than 10 minutes if the MRI machine is technically capable of doing it (e.g. automatic positioning of scans, fast diffusion scanning).

5. If ischaemic stroke is diagnosed, a follow-up CT examination is recommended to assess if haemorrhagic transformation was observed up to 48 hours [45–50].

Based on the distribution of ischaemic lesions, radiologists can identify the cause of a stroke in a child. Ischaemic strokes of cardiogenic aetiology are more often bilateral, occur in both the anterior and posterior circulations, and have an increased tendency for haemorrhagic transformation. Similarly, stroke caused by the herpes virus is multifocal but more frequently unilateral and related to limbic system and basal ganglia [51–54].

The radiological picture of ischaemic stroke depends mainly on its duration and the extent of ischaemia caused by the size of the occluded artery (e.g. internal cerebral artery *vs.* anterior cerebral artery) and the level of occlusion (e.g. occlusion of the first segment in the middle cerebral artery, so-called M1 *vs.* M4).

The time from the onset of clinical symptoms is the criterion for the division of the stroke into the following phases: hyperacute (0–6 hours; divided into the thrombolytic window: 0–4.5 hours and outside the thrombolytic window 4.5–6 hours), acute (6–24 hours), subacute (1–7 days), and chronic (8 days to 3 months).

In the first minutes of ischaemia, lactic acidosis develops and the cell membranes and the ion pump are damaged. This in turn leads to the redistribution of water from the extracellular to the intracellular space and the formation of cytotoxic oedema. Cytotoxic oedema in the infarction zone is visible as areas of restriction of free diffusion of water molecules in the extracellular space, i.e. high signal areas on DWI maps and low signal areas on apparent diffusion coefficient (ADC) maps.

Cytotoxic oedema lowers the brain tissue density in CT theoretically by 2 HU (Hounsfield units) within 2.5 hours, which can be difficult for the human eye to see and requires extensive experience in evaluating CT scans [55–56].

Paediatric stroke recommendations — qualification for mechanical thrombectomy [57–59]

This decision is made jointly by an interventional radiologist, a paediatric neurologist, and a neurologist from a centre experienced in treating patients with mechanical thrombectomy based on the following data: the age of the child, the time elapsed since the onset of clinical symptoms, the severity of clinical symptoms according to the MRS and NIHSS scales, the angio-CT examination/angio-MRI performed on the height of the aortic arch, and the advancement of ischaemic lesions on CT according to the ASPECTS scale (Alberta Stroke Programme Early Computed Tomography Score).

For MRI, the size of the lesion can be assessed using the approximate ASPECTS to DWI scale [60–70].

Standard considerations for qualifying adult ischaemic stroke patients for endovascular treatment with mechanical thrombectomy are as follows:

- up to 6 hours from the presentation of symptoms
- MRS = 0 or 1
- NIHSS = not less than 6
- ASPECTS = not less than 6
- occlusion or critical stenosis of a large arterial trunk documented in angio-CT or angio-MRI: ICA, MCA (M1, M2, ACA), BA, VA and changes at the junction of the above-mentioned arteries.

The ASPECTS scale used to quantify early ischaemic CT lesions identifies patients who will benefit from mechanical thrombectomy. According to this scale, the brain is divided into 10 areas of MCA supply, 1 point is scored for ischaemic changes in a single area. If there is ischaemia in several areas — the changes add up and the rating is weighted. In the case of a correct CT image in the MCA range, the brain CT image gets 10 points on the ASPECTS scale, when all 10 MCA territories are occupied — ASPECTS is 0 points, but when three areas are occupied — ASPECTS is 7. We only add up fresh ischaemic changes, ignoring the old ones. The MCA areas are set out in Figure 1.

In addition, an extended therapeutic window may be considered in children by considering the principles used in adults in the DEFUSE-3 and DAWN studies and in the absence of certain information at the time of onset according to the WAKE-UP protocol.

The DAWN study showed that adult patients with obstruction of the large cerebral artery and a small volume of infarcted area (reduced flow in CBF) and, at the same time, with a relatively large neurological deficit, may benefit from mechanical thrombectomy in the therapeutic window up to 24 hours after the onset of symptoms.

Similar conclusions can be drawn from the DEFUSE-3 study, in which the target mismatch profile on CT perfusion or MRI-mismatch between the volume of the penumbra area and ischaemic core volume was the basis for the qualification of patients for endovascular treatment of occlusion of the large arterial trunk 6–16 hours after the clinical manifestation of stroke. Volumetric assessment of an outbreak on DWI maps in the adult population in the DAWN study was used to qualify patients for endovascular therapy between six and 24 hours from the time they were last seen without clinical signs of stroke, outside the standard therapeutic window.

Patients with a relatively small volume of diffusion restriction and, at the same time, a significant neurological deficit, have been successfully treated with mechanical thrombectomy in an extended therapeutic window. Similar observations were made in the DEFUSE-3 study, where the decisive factor in endovascular restoration of the main arterial trunk 6–16 hours after the onset of the disease was a clear mismatch between the DWI and PWI sequences [27–36].

Although a fairly large number of randomised trials conducted in adults have found that they do benefit from mechanical thrombectomy, we cannot directly transfer these guidelines to children. Therefore, in each case, the assessment should be highly individualised, and we recommend thrombectomy therapies only in older children.

Summary

1. Neuroimaging on admission — CT or MRI in every child:
   a. CT of head without using contrast agent;
   b. Rapid MRI protocol including inversion and recovery sequences (FLAIR, fluid attenuated inversion recovery), MR diffusion-weighted imaging (DWI) with actual diffusion-weighted imaging (ADC, apparent diffusion coefficient) and T2 * or SWI;
2. In children with symptoms of ischaemic stroke on MRI/ /CT or with a normal CT image, it is recommended to perform angio-CT or angio-MRI of intracerebral arteries (from level of aortic arch);
3. Control neuroimaging of head (CT or MR) to exclude haemorrhagic transformation — usually performed 24 hours after start of thrombolytic treatment and/or mechanical thrombectomy, or performed earlier in event of significant deterioration of neurological condition.

An abbreviated method of neuroimaging diagnosis is presented in Figure 2.

Paediatric stroke recommendations — diagnostics of thrombophilia

The basic analysis includes blood group, complete blood count with microscopic smear and iron balance assessment, biochemical tests, and coagulation tests. Their implementation is also aimed at assessing the safety of anticoagulant/ /antiplatelet or thrombolytic therapy [70–72]. D-dimer is of limited importance in children, because the results are often false-positive (including infection, pre-laboratory errors), and a low concentration of D-dimer does not exclude a thromboembolic event, including ischaemic stroke [70–73].

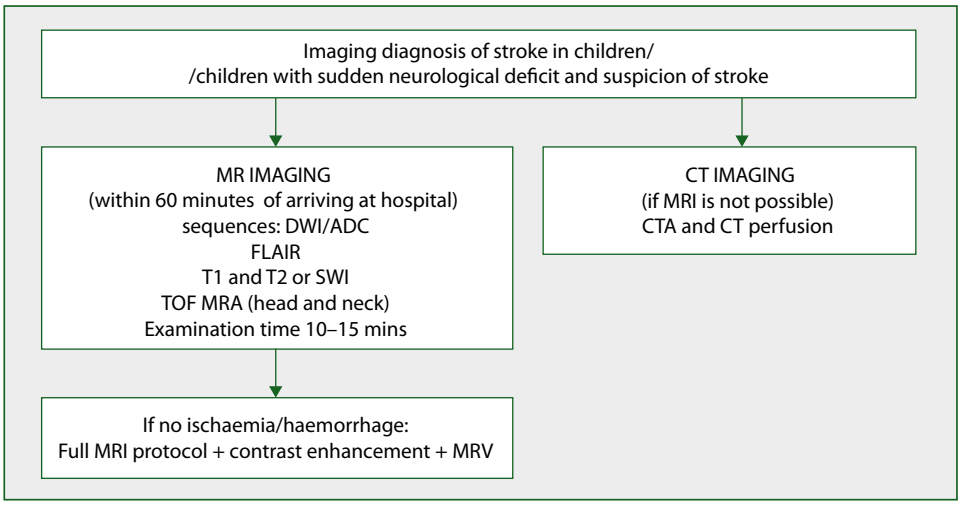

Figure 2. Imaging diagnosis of stroke in children/children with sudden neurological deficit and suspicion of stroke

In our opinion, laboratory tests for thrombophilia should be performed in every child diagnosed with ischaemic stroke, although experts in this field are not unanimous on this topic. The parameters set out in Table 2 are used in the differential diagnosis of hypercoagulability [71–77].

Important to consider

1. In the acute phase of stroke/thrombosis, the determination of proteins C, free S, antithrombin III, and activity of clotting factor VIII, can be inaccurate. If incorrect results are obtained, it is recommended to repeat them at least 6–8 weeks after the acute episode. Factor VIII is also an acute phase protein [74–76].
2. Determination of homocysteine level is recommended, and, only if elevated, polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene should be tested. Carriage of clinically insignificant MTHFR polymorphisms is common in the Caucasian race. Importantly, the increase in homocysteine concentration also occurs in vitamin deficiencies (folic acid, vitamins B6, B12) and in metabolic diseases such as homocystinuria or cobalamin C deficiency [75].
3. Antiphospholipid syndrome (APS) is the most severe acquired thrombophilia. It is most common in adolescents and young adults. The diagnosis and treatment of APS in children is based on the guidelines for adults (Tab. 2), and the criteria for paediatric patients are being drawn up [78–81]. Antiphospholipid syndrome comprises primary (isolated) and secondary (coexisting) APS, which is usually found in the course of rheumatological diseases (mainly systemic lupus erythematosus). After a bacterial or viral infection, as well as in patients with atopic dermatitis, antibodies typical for APS [anticardiolipin antibodies (aCL), anti-β2-glycoprotein I antibodies (anti- β2GPI); lupus anticoagulant (LA)] may be transient, and therefore it is necessary to repeat the tests after 12 weeks. It should be emphasised that in a group of 121 children from the Ped-APS Registry, ischaemic stroke was the first manifestation of APS in 31 children [80]. In the case of perinatal/ /neonatal stroke, the role of maternal antiphospholipid antibodies penetrating the placenta is ambiguous, and additional factors (including perinatal hypoxia, infection, and congenital thrombophilia) seem to play a role in the development of stroke [83].
4. Oral contraception, or increased activity of factor VIII, are associated with acquired activated protein C resistance (APCR) [70–75].
5. In the case of ischaemic stroke in a patient with sickle cell anaemia, the RCPCH 2017 recommendations discuss in detail the management and different treatment for this group of patients [15].

Tests for thrombophilia screening are set out in Table 3.

Diagnostic criteria for the antiphospholipid syndrome recommendations in Table 3 [78].

Paediatric stroke recommendations — other laboratory tests

An important element of the diagnosis of the aetiology of stroke, apart from neuroimaging tests, are laboratory tests that should take into account haematological disorders that predispose people, especially children, to the occurrence of a stroke. Additional tests should exclude the inflammatory process, systemic diseases, disorders of lipid and electrolyte metabolism, as well as mitochondrial diseases or infection [6, 37]. Most of these tests can be performed in the days following acute illness.

If an infection is suspected, a chest X-ray should be performed, and if an inflammatory aetiology of ischaemic stroke

Table 3. Diagnostic criteria for antiphospholipid syndrome [77]

Clinical criteria:
Venous or arterial thrombosis confirmed by imaging tests
Obstetric failures:
— death of a morphologically normal foetus > 10 weeks of gestation
— premature birth of a morphologically normal child < 34 weeks gestation due to eclampsia, severe pre-eclampsia or confirmed placental insufficiency
— three or more spontaneous abortions < 10 weeks gestation, other causes excluded
Laboratory criteria:
Lupus anticoagulant confirmed at least twice with an interval of ≥ 12 weeks
Anticardiolipin antibodies (IgG and/or IgM) in medium or high titre (> 40 GPL or MPL*, or > 99 percentile), confirmed at least twice at an interval of ≥ 12 weeks
Antibodies against β2-glycoprotein I (in IgG and/or IgM class), titre > 99th percentile, confirmed at least twice with an interval of ≥ 12 weeks)

*At least one clinical criterion and one laboratory criterion are required for diagnosis
*Symbols GPL and MPL denote standardised units used in measurement of anti-cardiolipin antibodies in IgG and IgM classes, respectively

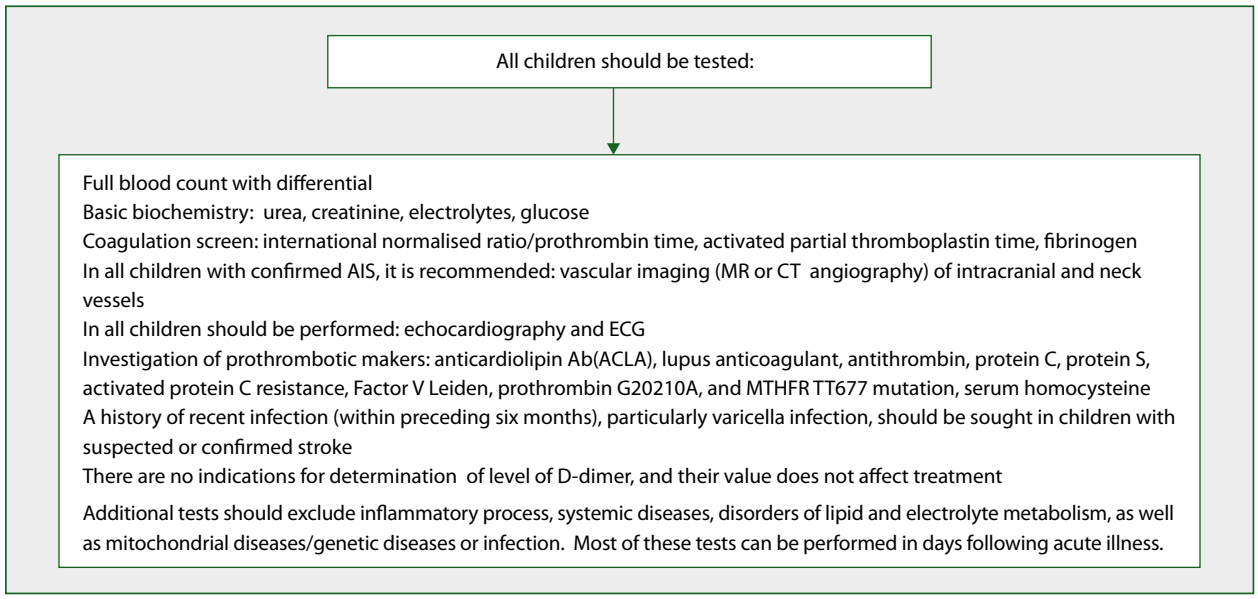

Figure 3. Investigations for suspected or confirmed childhood stroke

or subarachnoid haemorrhage is suspected, a cerebrospinal fluid test is performed if the CT image is abnormal.

If there are seizures or non-seizure status epilepticus, electroencephalography (EEG) should be performed. If possible, this should be performed in a child at the beginning of the disease, in order to be able to follow the dynamics of changes in subsequent tests, which may be a possible indicator of the development of epilepsy. Every child with suspected stroke should have the following test (Fig. 3).

Paediatric stroke recommendations — Doppler ultrasound of vessels in children

This test should be performed in all children who have had a stroke or transient ischaemic attack, regardless of other neuroimaging tests [86].

Probes used in ultrasound examinations

Examination of extracranial and intracerebral arteries should be performed with a duplex-Doppler apparatus, a 5–13 MHz linear probe, which enables the assessment of the vessel wall, as well as the assessment of flow in the form of colour-coded flow according to velocity or amplitude (the so-called 'power Doppler'), with an assessment of the flow direction and velocity graph (Doppler spectrum in visualisation of the spectrum shape and measurement of systolic and diastolic velocities as well as vascular resistance coefficients).

The transcranial examination can be performed using Transcranial Doppler ultrasonography (TCD), sometimes called 'blind Doppler', equipped with a 2 MHz pulse wave (PW) probe) or duplex-Doppler examination with a sector probe with a frequency of 2–3.5 MHz. The lower frequency

used in transcranial probes makes it impossible to assess the walls of intracranial vessels, so the most important thing is to assess the velocity, flow direction and shape of the Doppler spectrum.

In very young children with an open fontanelle, convex duplex probes with a small forehead area, broadband with a frequency of 5–11 MHz is used. The examination is routinely performed through the anterior fontanelle [87].

Paediatric stroke recommendations — cardiological diagnostics

A cardiogenic stroke is an ischaemic stroke caused by embolic material formed in the cavities or valves of the heart. In the general population, cardiogenic stroke accounts for 25–30% of all ischaemic strokes. With age, the proportion of cardiogenic strokes in the pathomechanism of ischaemic stroke increases, and it reaches 50% in the 45–80 age group. This is due to the increase in potential risk factors, such as: an increase in the percentage of cardiac arrhythmias (mainly atrial fibrillation), dilated and contractile disorders of the heart cavities, and valve prostheses as well as venous flow disorders, which can lead to the formation of embolic material and its subsequent migration into cerebral circulation in the mechanism of paradoxical (cross) embolism. Such a mechanism of stroke is favoured by impaired venous flow and inflammation of these vessels, which predisposes to the formation of embolic material in them. The incidence of these diseases increases significantly with age.

A large percentage of strokes are cryptogenic strokes with an undiagnosed cause. It depends, of course, on the scope and detail of the conducted diagnostics. The causes and pathomechanisms of cardiogenic stroke in the paediatric population are completely different. The disease entities that are the main causes of stroke in adults (atrial fibrillation and dilated cardiomyopathy) are almost entirely absent in the paediatric population. In an analysis of 667 children with ischaemic stroke, 30.6% were diagnosed with heart disease. Congenital heart defects were found in 59.3%, acquired cardiovascular abnormalities in 19.6%, and PFO (patent foramen ovale) in 15.2% [88].

There is an increased risk of cardiogenic stroke in children with congenital heart disease. Defects with a right-to-left leak (e.g. Fallot syndrome) allow the embolic material to pass from the venous system to the systemic circulation through the existing communication. The formation of embolic material is favoured by compensatory polyglobulia, which occurs in response to cyanosis accompanying the defect.

A similar situation occurs in patients with Eisenmenger's syndrome, in whom changes in the pulmonary vessels in the course of the defects with increased pulmonary flow leads to the development of pulmonary hypertension and right-left reversal of the intracardiac shunt. Also, children after cardiac surgery for heart defects have an increased risk of thrombotic material formation, which is facilitated by the presence of artificial materials used during the correction of the defect. This thrombotic material can be clots or bacterial vegetations.

Bacterial endocarditis, especially located on the valves or structures of the left heart, is associated with a high (25–50%) risk of stroke [89]. Compared to the general population, the risk of ischaemic stroke in young adults with a heart defect is 9–12 times higher, and in children up to 19 times higher [90–91]. Studies of more than 25,000 children and young adults with congenital heart disease have shown that the incidence of ischaemic stroke is 0.5%, which is 11 times higher than in the general population [92].

Heart defects predisposing to ischaemic stroke in the mechanism of paradoxical embolism include atrial septal defect (ASD II). This defect causes blood to flow from the left to the right heart. However, the pressure difference between the atria is small. In certain situations, the leak direction may be reversed temporarily. This can cause the transfer of embolic material to the systemic circulation. A history of ischaemic stroke in this mechanism is an indication for the closure of the interatrial defect, regardless of its size and haemodynamic significance. A similar mechanism of stroke may occur in the case of patent foramen ovale (PFO). This remnant of the foetal circulation remains patent in up to 20–30% of the population. It is not treated as a heart defect, and under no circumstances is there any indication for its prophylactic closure. Due to the anatomy of PFO, spontaneous leakage of blood between the atria is often not observed, or the flow is haemodynamically insignificant.

However, in situations such as pushing, sneezing, lifting heavy objects, or Valsalva's manoeuvre, right-left blood flow may occur, and with it, embolic material may enter the systemic circulation. In patients after ischaemic stroke and after excluding its other causes, patent foramen ovale may be considered as a potential site for the transition of the embolic material from the venous to the systemic circulation.

In people under 45 years, as many as half of ischaemic strokes may be caused by a paradoxical embolism. In this age group, percutaneous PFO closure can be considered as a secondary prophylaxis of stroke. However, in paediatric patients, this embolic mechanism is much less frequent. This is mainly due to the fact that venous thrombosis as a potential source of embolism occurs rarely in children, with a frequency of 0.05/1,000/year [93].

Data from the literature shows that in children after an ischaemic stroke of uncertain origin, the incidence of PFO is higher than in the adult population, and in many of them the decision has been made to percutaneously close the PFO [94–97]. Implantation of the device closing interatrial communication is a safe and effective method of treatment also in paediatric patients.

Arterio-venous fistulas located in the lungs may be another cause of ischaemic stroke in the mechanism of paradoxical embolism. The prevalence of arteriovenous fistulas in the lungs is estimated at 2–3/100,000. More than 80% of fistulas are congenital and often coexist with Rendu-Weber-Osler syndrome. Fistulas are abnormal connections between the artery and the pulmonary vein, bypassing the pulmonary capillaries, in which there is a constant flow of desaturated blood from the pulmonary bed directly into the pulmonary veins, bypassing the capillaries. Fistulas can cause desaturation (cyanosis), volume overload, or be asymptomatic. Ischaemic stroke in the mechanism of paradoxical embolism may be the first, and often the only, symptom. The frequency of strokes in pulmonary arteriovenous fistulas is estimated at 18–32%, and up to 60% in the case of multiple fistulas [98].

The risk of paradoxical embolism is increased by the fact that there is constant right-left blood flow. Percutaneous embolisation of abnormal connections is the method of choice for the treatment of these malformations. This allows for minimally invasive, precise closure of them while maintaining healthy lung tissue. Valsalva contrast echocardiography is standard in the diagnosis of leaks between the right and left hearts. During echocardiography, saline is administered intravenously with microbubbles in the air. During the Valsalva test, it is found that the micro air vesicles enter the systemic circulation.

Transoesophageal echocardiography is the most sensitive and specific. However, in children with good echocardiographic visualisation, a transthoracic examination is sufficient. Equally sensitive is the transcranial Doppler (TCD) test, also with agitated saline. During the Valsalva manoeuvre, the micro signals are detected in the cerebral circulation. This examination, although simpler and less invasive for the patient, does not allow for the indication of the leakage site, and only detects its presence. It can definitely be used as a screening test.

Paediatric stroke recommendations — anticoagulant treatment and secondary prevention of stroke in children, based on RCPCH 2017 and AHA 2019 guidelines

1. If patient is qualified for thrombolytic treatment according to scheme included in these recommendations, antiplatelet/ /anticoagulant treatment is postponed for 24 hours [35].
2. Patients who do not qualify for thrombolytic therapy should be urgently initiated on antiplatelet therapy (in absence of CNS bleeding and other contraindications) [36]. Recommended therapy is acetylsalicylic acid (ASA) at a dose of 5 mg/kg (up to a maximum of 300 mg daily) with dose reduction after 14 days (up to a maximum of 75 mg daily) [35, 71, 72].
3. Patients with a suspected cardiovascular or vascular embolism should be treated with anticoagulation (low molecular weight heparin/unfractionated heparin/vitamin K antagonist; in the absence of contraindications and intracranial bleeding) [35, 71–72]. Anticoagulation therapy should last at least six weeks (in the case of dissection of the arteries) or longer. A multi-specialist council and planning of further therapy, including procedures in the field of invasive cardiology, is necessary [36, 72, 98].

It must be emphasised that the main goal of antiplatelet or anticoagulant therapy is to prevent recurrence of stroke [35, 71–73].

Safety of therapy

Patients with a massive ischaemic stroke involving a significant area of the brain (> 2/3 of the vascular territory of middle cerebral artery), or with arterial hypertension, are at high risk of secondary haemorrhage. The decision whether to initiate anticoagulant/antiplatelet therapy should be postponed for up to 72 hours. Patients with middle cerebral artery involvement may develop a malignant cerebral oedema requiring urgent neurosurgical treatment (hemicraniectomy) and reversal of anticoagulant drugs [35, 71–73].

During antiplatelet therapy with ASA, in case of severe epistaxis or gastrointestinal intolerance, it is recommended to reduce the dose to 1–3 mg/kg/day. ASA therapy is advised to last at least two years, because the risk of recurrent stroke is highest during this period. ASA therapy is considered safe, and so far Reye's syndrome has not been reported in children receiving the drug in a prophylactic dose [99].

Based on the observation of large groups of patients, the risk of secondary haemorrhage in ischaemic lesions in children who have received or have not received antiplatelet/anticoagulant therapy is similar [100–102]. The same observations also apply to newborns treated with anticoagulants due to cardiogenic strokes [101].

Paediatric stroke recommendations — indications for use of chronic secondary anticoagulant prophylaxis after ischaemic stroke [103–105]:

- Recurrent ischaemic stroke
- Predisposing heart defect, arrhythmias, blood vessels abnormalities
- Antiphospholipid syndrome
- Severe thrombophilia: deficiency of antithrombin, protein C deficiency, free protein S deficiency, homozygous factor V Leiden mutation, homozygous G20210A mutation in prothrombin gene

- Complex thrombophilia (e.g. coexistence of heterozygous forms of factor V Leiden mutation and prothrombin gene G20210A and others)
- Current process/inflammation in body predisposing to relapse (e.g. active nephrotic syndrome, active ulcerative colitis, use of asparaginase).

Long-term anticoagulants in children are vitamin K antagonists (VKA) administered orally (e.g. warfarin, acenocoumarol) or subcutaneously injected low molecular weight heparin when the use of VKA is impossible (gastrointestinal malabsorption, in tablet form in young children). Therapy requires regular monitoring, including INR or anti-Xa determination, respectively. In 2022, the direct oral anticoagulant (DOAC) rivaroxaban was approved for use in children in Poland in the treatment of VTE and prevention of its recurrence, while other DOACs are yet to be registered in patients under 18.

Studies in adults have shown that DOACs should not be used in patients with antiphospholipid syndrome or in patients undergoing heart valve replacement (due to the increased frequency of recurrence of thrombosis) [105].

The risk of recurrent ischaemic stroke and, on the other hand, the risk of bleeding, the chronicity and the burden of secondary anticoagulation in children raise many doubts. To make therapeutic decisions, specialist consultations and the active participation of the patient and his or her family are necessary.

Paediatric stroke recommendations — intravenous thrombolytic therapy

Intravenous thrombolytic therapy of ischaemic stroke (*i.v.* cerebral thrombolysis) with tissue plasminogen activator (rt-Pa *i.v.*) has been approved for the treatment of adult patients since 1996, initially in the USA based on results from the National Institute of Neurological Diseases and Stroke (NINDS), and then since 2002 in Europe, following the results of randomised clinical trials and the European Cooperative Acute Stroke Study (ECASS) [106].

In Poland, cerebral thrombolysis, implemented incidentally since the beginning of the 21st century, has been admitted into routine clinical practice since 2003 and is currently used in an average of 17%, and in the best patient centres more than 33%, of ischaemic stroke patients. Even though access to endovascular methods is increasingly common, rt-Pa *i.v.* remains a standard method of treatment of stroke patients [107].

The insufficient data on safety and long-term effects can probably be explained by the fact that the US Food and Drug Administration and Health Canada do not recommend thrombolytic therapy for ischaemic stroke in children and adolescents. Also, the American Heart Association, the American Stroke Association, and the American College of Chest Physicians do not recommend routine use of thrombolytic therapy for stroke before the age of 18 [36].

The opinion of the American Heart Association/American Stroke Association on the management of stroke in newborns and children, published in 2019, states that it remains controversial, without providing clear indications/contraindications for the use of thrombosis brain due to the absence of clinical trial results on the treatment of acute phase of stroke. The AHA/ASA recall only the protocol elements used in the TIPS (Thrombolysis in Paediatric Stroke) study (classic rt-PA dosing at a dose of 0.9 mg/kg body weight: 10% by bolus in the first 5 minutes, the remaining amount in the infusion pump within 55 min) [108].

Currently, the most detailed practical guidance is provided by the algorithm proposed by the Boston Children's Hospital Neurological Department, prepared on the basis of the TIPS study protocol (Tab. 2) [8]. Similarly, the Australian Clinical Consensus Guidelines for diagnosis and acute management appropriate in specific children proposes the use of criteria based on the TIPS study consensus, pointing to "weak" evidence of the benefits of thrombolytic therapy in children [7].

In a small group of patients, it is additionally helpful to use the premises contained in the summary of product characteristics of actilyse/alteplase, indicating: "in children ≥ 16 years of age, the individual benefit-risk ratio should be carefully assessed. Children aged ≥ 16 years should be treated according to the guidelines for adults after confirmation of arterial ischaemic thromboembolism (exclusion of a disease imitating stroke)" [108].

In light of the above facts, thrombolytic therapy in children and adolescents < 16 years of age can still be performed outside the registration indications (only off-label), and therefore should be considered individually and after a detailed consideration of the benefit-risk ratio. Its conduct should be carried out in a centre equipped with an interdisciplinary team of specialists experienced in the diagnosis and treatment of stroke in children and adolescents.

Indications and contraindications for cerebral thrombolysis in children and adolescents proposed in TIPS study [109]

Indications

- Age: 2–17 years
- Symptoms of acute ischaemic stroke defined as sudden onset of focal deficit
- NIH Stroke Scale (PedNIHSS) ≥ 4 and ≤ 24 points (Annex 1) [110]
- Duration of symptoms < 270 minutes
- Features of acute ischaemia confirmed by neuroimaging:
  - MRI with diffusion-weighted sequences and MRA showing at same time signs of partial or complete occlusion of cerebral arterial vessel in location corresponding to symptoms,

- CT examination showing correct image of brain structures or minimal early ischaemic changes and CT-angio examination showing partial or complete obstruction of cerebral arterial vessel in location corresponding to symptoms,
- Exclusion of haemorrhagic foci.

Contraindications*

- Unknown time of onset
- Pregnancy
- Clinical symptoms suggesting a subarachnoid haemorrhage even with a normal CT imaging
- Patients in whom consent has not been obtained for a potential blood transfusion
- Previous intracranial haemorrhage
- Known arteriovenous malformation, aneurysm or brain tumour
- Systolic blood pressure in lying or sitting position > 15% higher than 95th percentile value for patient's age
- Blood glucose < 50 mg/dL (2.78 mmol/L) or > 400 mg/dL (22.22 mmol/L)
- Platelet count < 100,000, PT > 15 sec, INR > 1.4, PTT > laboratory norm
- Symptoms of myocardial infarction or pericarditis that require a cardiac evaluation
- Stroke, major head injury, or intracranial surgery in previous three months
- Major surgery or biopsy within previous 10 days (relative contraindication)
- Bleeding from gastrointestinal tract or urinary tract during previous 10 days (relative contraindication)
- Puncture of artery in a place inaccessible to pressure or lumbar puncture in period of seven preceding symptoms (relative contraindication) (patients with a catheter inserted into pressure artery are not excluded)
- Patients with active neoplastic disease or within one month after end of treatment
- Patients with known significant coagulation deficits (patients with mild platelet dysfunction, mild von Willebrand's disease, or other mild coagulation deficits are not excluded)
- Mild neurological deficit (PedNIHSS < 4) at initiation of rt-PA infusion or prior to initiation of sedation for neuroimaging (if applicable)
- Significant neurological deficit suggesting extensive territorial stroke (PedNIHSS > 24 points), regardless of size of ischaemic focus seen in neuroimaging
- Symptoms of stroke in course of bacterial endocarditis, moya moya disease, sickle cell anaemia, meningitis, myeloid, air or fat embolism
- Previously diagnosed primary central nervous system vasculitis (PACNS) or secondary central nervous system vasculitis (childhood focal cerebral arteriopathy (FCA) is a contraindication)
- Intracranial haemorrhage (HI-1, HI-2, PH-1 or PH-2) demonstrated by MRI or CT of head
- Dissection of intracranial arteries (above exit of eye artery)
- Significant volume of infarct on MRI, covering > one third of MCA supply area
- Known allergy to recombinant plasminogen activator
- INR > 1.4
- APTT in laboratory standard for heparin treatment up to 4 hours
- LMWH treatment in previous 24 hours (aPTT and INR do not reflect LMWH effect).

*The occurrence of an epileptic seizure upon onset is not a contraindication if the other inclusion criteria are met and if the exclusion criteria are absent.

Paediatric stroke recommendations — malignant MCA syndrome

Malignant middle cerebral artery syndrome (MMCAI) is a situation where the ischaemic area is large and covers over 33% of the MCA vascularisation range, which is associated with large swelling of the brain and rapid deterioration of the patient's condition. MMCAI risk factors include seizures lasting more than 5 minutes as a manifestation of trauma, and a severe neurological condition at the beginning. For adult patients with MMCAI, the recommended management is to perform a decompressive craniectomy; this improves the survival rate of the stroke and the neurological outcome of patients in long-term follow-up; in the case of children, there is no reliable research [8, 36]

In summary, we propose a scheme illustrating in a simplified way the diagnostic procedure in the case of a child with suspected stroke (Fig. 4).

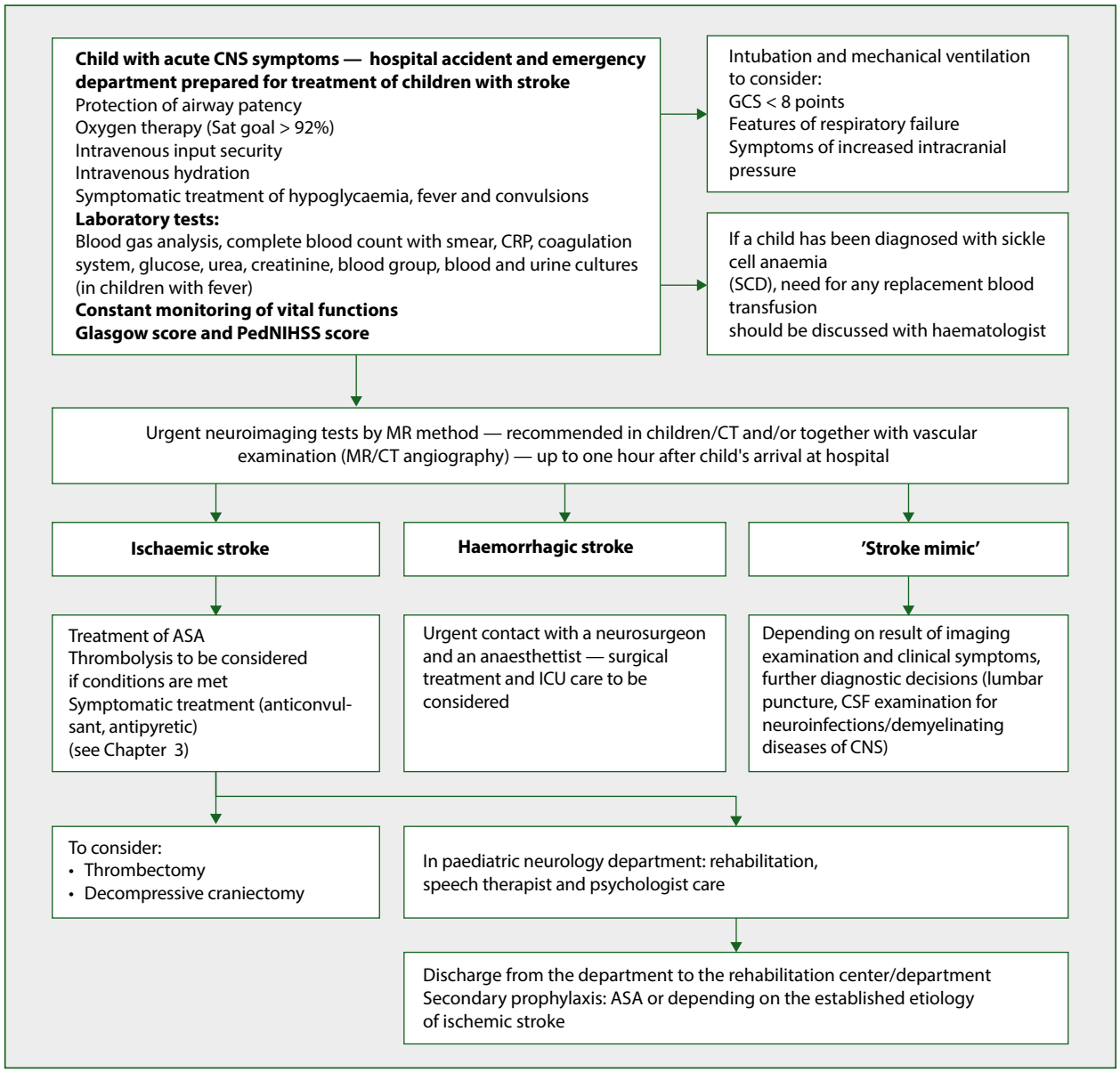

Figure 4. Scheme of management of child with acute symptoms of central nervous system/suspected acute cerebrovascular disease — from appearance of symptoms through diagnosis and treatment of acute phase to secondary prophylaxis (according to Royal College of Paediatrics and Child Health recommendations in 2016, 2019 [8, 36], modified by the authors)

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