Recanalization strategies in childhood stroke: a 3-year surveillance study in Germany

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Abstract

Objective

Childhood acute ischemic stroke (CAIS) is a rare event. Diverse etiologies, risk factors, symptoms and stroke mimics hamper obtaining a fast diagnosis and implementing immediate recanalization strategies.

Methods

Over a period of 3 years (2015–2017), the data of 164 pediatric patients (> 28 days of life–18 years) with a first episode of AIS were submitted to a hospital-based nationwide surveillance system for rare disorders (ESPED). We report a subgroup analysis of patients who have undergone recanalization therapy and compare these data with those of the whole group.

Results

Twenty-eight patients (17%) with a median age of 12.2 years (range: 3.3–16.9) received recanalization therapy. Hemiparesis, facial weakness and speech disturbance were the main presenting symptoms. The time from onset of symptoms to confirmation of diagnosis was significantly shorter in the intervention group (4.1h vs. 20.4 h, $p = < 0.0001$). Only in one patient occurred a minor bleed. Cardiac disease as predisposing risk factor was more common in the recanalization group.

Conclusion

Recanalization therapies are feasible and increasingly applied in children with AIS. High awareness, timely diagnosis and a large amount of expertise may improve time to treatment and make hyperacute therapy an option for more patients improving their outcomes.

Introduction

Childhood arterial ischemic stroke (CAIS) in children aged older than 28 days of life and up to 18 years is a rare event, with an incidence of approximately 1–8/100,000 children/year.[1–3] Time delay in diagnosing CAIS has been a greatly challenging issue over several years. Increased awareness, implementing pediatric stroke protocols and algorithms has led to faster diagnoses, and therefore, more patients have become eligible for potential recanalization therapies.[4–6] Nevertheless, the diagnosis and treatment of CAIS remains challenging due to the existence of a multitude of stroke mimics and different predisposing risk factors, such as arteriopathy, thrombophilia, cardiac disorders, metabolic disorders or cancer.[7, 8] Several case series have demonstrated the feasibility of intravenous thrombolysis, but a prospective randomized trial failed due to recruiting problems (small patient number and presence of contraindications for recanalization therapy (RT))[9]. Moreover, long-term outcome data are lacking.[10–12] In contrast to adult stroke management a different point of view for childhood AIS is necessary: (a) arteriopathy is one of the most common causes of CAIS, (b) arteriopathy increases the risk of interventional complication (as dissection, bleeding etc.)[13] (c) distinctive features of developmental hemostasis, such as lower plasminogen (PA) and higher plasminogen activator inhibitor 1 (PAI1) levels in infants, (d) the supposed lower effectiveness of standard recombinant tissue plasminogen activator (rt-PA) doses,[10–12, 14, 15] and (e) the presumed lower bleeding risk in children than in adults.[16] Since 2015 positive results of several studies for endovascular treatment of adult stroke have raised the question of whether thrombectomy is also feasible in pediatric stroke.[17–19] Additionally, the Dawn [20] and Defuse [21] Trial suggest larger treatment windows in adults and may further increase the number of eligible children with AIS despite longer delay from last time seen well and time of diagnosis.

Although randomized controlled trials addressing the efficacy of such treatment modalities are lacking, several case series have concluded that endovascular procedures are feasible also in children.[22–27]

Based on active surveillance of childhood stroke in Germany (Gerstl et al 2019),[28] we aimed to investigate the rate and characteristics of patients treated with recanalization therapies (RTs). In this subgroup analysis, differences in symptoms, time gaps, factors triggering a time gap compatible with a hyperacute RT (within 6h after the onset of symptoms) and short-term outcome will be outlined.

Results

Between 01/01/2015 and 12/31/2017, 164 patients with CAIS were reported to ESPED (26). 17.1% ($n = 28$) of patients with a median age of 12.2 years (range: 3.3–16.9) received hyperacute RT with either thrombolysis ($n = 10$), thrombectomy ($n = 10$) or both ($n = 8$). In the recanalization group, more patients were older than five years than in the entire cohort (89% vs. 62%, $p = 0.005$). Only three patients were younger than five years (3.3, 4.1 and 4.5 years old). Similar to the whole study group, we observed a male preponderance (m:w, 1.8:1) in the subgroup analysis. Twenty-seven patients were Caucasian (one Asian). Table 1 summarizes patient characteristics for the whole group and for the recanalization and non-recanalization groups, and Table 2 shows the detailed overview for each patient in the recanalization group.

Table 1
PATIENT CHARACTERISTICS

	PATIENT CHARACTERISTICS						p-value
	All patients (N = 164)		Patients who did not undergo recanalization		Patients who underwent recanalization		
	(N = 136)		(N = 28)				
	n	(%)	n	(%)	n	(%)	
General characteristics							
Sex	164	97 (59)	136	79 (58)	28	18 (64)	0.54
male	164	67 (41)	136	57 (42)	28	10 (36)	0.005
female	164	9.1 ± 6.0	136	8.4 ± 6.1	28	12.271 ± 4.2	0.004
Age [in years, at symptom onset]	154	109 (67)	127	84 (62)	27	25 (89)	0.12
Age ≥ 5 years	164		136	115 (91)	28	27 (100)	0.99
Caucasian ethnicity		142 (92)		29 (21)		6 (21)	
Stroke, thrombosis or other stroke-related events in family		35 (21)					
Time							
Time from symptom onset to confirmation of diagnosis [in h]	82	37 (45)	58	16 (28)	24	21 (88)	< 0.0001
< 4.5 h		2 (2)		2 (4)		0 (0)	
4.5 h to < 6 h		11 (13)		9 (16)		2 (8)	
6 h to < 12 h		32 (39)		31 (53)		1 (4)	
≥ 12 h							
Short-term outcome							
Death	161	4 (2.4)	133	3 (2.2)	28	1 (3.6)	0.54
Diagnosis at discharge:	164	69 (42)	136	55 (40)	28	14 (50)	0.35
Hemiparesis		24 (15)		19 (14)		5 (17)	0.77
Facial palsy		19 (12)		15 (11)		4 (14)	0.75
Speech disturbance		11 (7)		11 (8)		-	0.21
Seizure		6 (4)		6 (4)		-	0.59
Cerebellar symptoms		4 (2)		4 (3)		-	1.00
Visual disturbance							
Complications							
Bleeding	164	1 (0.6)	136	-	28	1 (3.6)	0.07
Cerebral edema		1 (0.6)		-		1 (3.6)	
Others		1 (0.6)		1 (0.7)		-	
Quantitative variables are expressed as mean ± standard deviation. Categorical variables are expressed as n (%). Test for differences between patients with recanalization vs. patients without recanalization: P-values are obtained from chi-square or fisher exact tests for categorical data and from Wilcoxon rank sum test for continuous variables							
Patient characteristics for the whole group (n = 164) and the subgroups of patients that did not (n = 136) and did undergo recanalization therapy (n = 28)							

Table 2
INDIVIDUAL PATIENT CHARACTERISTICS

Nr	Sex	Age [in years]	Onset of Symptoms	State of consciousness at admission	Onset of symptoms to confirmation of diagnosis [in hours]	Symptoms	Risk factor categoies	RT*	Affected vessels	Complications	Sh out
1	female	15.8	acute (within minutes)		4.	hemiparesis, headache, facial weakness, speech disturbance	others	L + T	middle cerebral artery		her
2	male	8.6	unclear	coma	3.	hemiparesis, headache, decreased consciousness level	cardiac arteriopathy	T			her
3	male	3.3	abrupt (within seconds)		1.2	hemiparesis, facial weakness	cardiac	L + T	middle cerebral artery		
4	female	14.1	acute (within minutes)	stuporous no orientation	3.3	hemiparesis, headache, facial weakness, decreased consciousness level, speech disturbance	prothrombotic state chronic head/neck disorders	L + T	middle cerebral artery posterior cerebral artery		
5	male	15.4	acute (within minutes)	dizzy no orientation	2.8	hemiparesis, facial weakness, decreased consciousness level, speech disturbance, vertigo	cardiac	L + T			her
6	female	4.1	acute (within minutes)	Stuporous no orientation	9.6	visual disturbance, headache, seizure (generalized), decreased consciousness level, vomiting/ nausea	chronic head/neck disorders	T			
7	male	15.6	abrupt (within seconds)		3.5	hemiparesis, facial weakness, speech disturbance	prothrombotic state	L			
8	male	15.9	acute (within minutes)		2.6	headache, ataxia, speech disturbance, dysdiadochokinesis	cardiac	L	middle cerebral artery		spe dis
9	male	9.7	abrupt (within seconds)		2.2	hemiparesis, visual disturbance, visual disturbance, headache, facial weakness, speech disturbance	cardiac	L	middle cerebral artery		her
10	female	14.1	acute (within minutes)	dizzy no orientation	2.1	hemiparesis, decreased consciousness level, speech disturbance	cardiac	L + T	middle cerebral artery		her
11	female	15.	abrupt (within seconds)	dizzy	2.8	hemiparesis, facial weakness, decreased consciousness level, speech disturbance, vertigo	cryptogenic	L	middle cerebral artery		spe dis
12	male	15.1	acute (within minutes)		.	hemiparesis	cryptogenic	L			

Characteristics of each patient in the recanalisation group (n = 28): *RT = recanalisation therapy, L + T = thrombolysis and thrombectomy, L = only thrombolysis only thrombectomy

Nr	Sex	Age [in years]	Onset of Symptoms	State of consciousness at admission	Onset of symptoms to confirmation of diagnosis [in hours]	Symptoms	Risk factor categoies	RT*	Affected vessels	Complications	Sho out
13	male	14.6	acute (within minutes)		2.5	hemiparesis	prothrombotic state	L	middle cerebral artery		her
							arteriopathy				
14	male	13.	acute (within minutes)		1.3	hemiparesis, headache, facial weakness, speech disturbance	prothrombotic state	L + T			her
15	female	5.5	progressive (within hours)		.	ataxia	chronic head/neck disorders	T			spe dis
16	male	16.9	abrupt (within seconds)	dizzy	2.	ataxia, decreased consciousness level, vertigo, vomiting/ nausea	Cardiac	L			
17	male	10.3	progressive (within hours)		28.	paresthesia, numbness feeling	prothrombotic state acute systemic	T	posterior cerebral artery		
18	female	15.6	acute (within minutes)		3.7	hemiparesis, facial weakness, seizure, speech disturbance	Cardiac prothrombotic state	T	middle cerebral artery		
19	male	11.4	progressive (within hours)	dizzy no orientation	3.	hemiparesis, facial weakness, speech disturbance, paresthesia	cardiac	T	middle cerebral artery		de
20	male	15.5	abrupt (within seconds)		1.3	hemiparesis, facial weakness, speech disturbance	Cardiac	T	middle cerebral artery		
21	male	15.1	abrupt (within seconds)		1.4	hemiparesis, facial weakness, speech disturbance	Cardiac	T	middle cerebral artery		
22	female	9.1	abrupt (within seconds)		3.5	ataxia, speech disturbance, apraxia	prothrombotic state	L	middle cerebral artery posterior cerebral artery		
23	male	13.7	acute (within minutes)	coma no orientation	2.5	hemiparesis, facial weakness, speech disturbance, splay foot position	cardiac prothrombotic state	L	middle cerebral artery		
24	male	6.9	acute (within minutes)	coma	8.	hemiparesis, facial weakness, seizure (focal), decreased consciousness level, speech disturbance	prothrombotic state hemato- oncological	T	middle cerebral artery		spe dis

Characteristics of each patient in the recanalisation group (n = 28): *RT = recanalisation therapy, L + T = thrombolysis and thrombectomy, L = only thrombolys only thrombectomy

Nr	Sex	Age [in years]	Onset of Symptoms	State of consciousness at admission	Onset of symptoms to confirmation of diagnosis [in hours]	Symptoms	Risk factor categories	RT*	Affected vessels	Complications	Sh out
25	male	4.5	abrupt (within seconds)	dizzy	1.	hemiparesis, facial weakness, speech disturbance	cardiac	T	middle cerebral artery		
26	male	16.2	acute (within minutes)		2.6	hemiparesis, facial weakness, speech disturbance	cryptogenic	L			her
27	female	15.2	unclear	coma	.	hemiparesis, headache, neglect	prothrombotic state	L + T	middle cerebral artery	cerebral edema	her
28	female	10.3	progressive (within hours)	stuporous	.	hemiparesis, headache, facial weakness, decreased consciousness level, vomiting/ nausea	cardiac	L + T	middle cerebral artery	bleeding	
Characteristics of each patient in the recanalisation group (n = 28): *RT = recanalisation therapy, L + T = thrombolysis and thrombectomy, L = only thrombolysis only thrombectomy											

Similar to the whole study group, hemiparesis (79%), facial weakness (61%) and speech disturbance (64%) were the leading presenting symptoms in the recanalization group. The simultaneous occurrence of all three symptoms was significantly more often present in the RT group than in the non-RT group (15 (62.5%, n = 24) vs 15 (14.4%, n = 104), $p = 0.0001$). Additionally, the RT group included facial weakness and speech disturbances as presenting symptoms significantly more often than the non-RT group ($p = 0.0003$, $p = 0.007$, respectively) (Table 3). Among patients older than 5 years (n = 107), visual disturbances were more frequent in the recanalization group than in the whole group ($p = 0.049$).

Table 3
PRESENTING SYMPTOMS

	All patients (n = 164)	Patients who did not undergo recanalization (n = 136)	Patients with recanalization (n = 28)	p-value
<i>Focal symptoms</i>	149 (91)	121 (89)	28 (100)	0.11
Hemiparesis	110 (67)	88 (65)	22 (79)	0.16
Facial weakness	52 (32)	35 (26)	17 (61)	0.0003
Speech disturbance	68 (41)	50 (37)	18 (64)	0.007
Visual disturbance	32 (20)	29 (21)	3 (11)	0.30
Ataxia	24 (15)	20 (15)	4 (14)	1.00
Paresthesia	19 (12)	17 (13)	2 (7)	0.66
Other focal symptoms	29 (18)	25 (18)	4 (14)	0.84
<i>Nonspecific symptoms</i>	79 (48)	65 (48)	14 (50)	0.83
Headache	39 (34)	30 (22)	9 (32)	0.25
Decreased consciousness level	34 (21)	25 (18)	9 (32)	0.10
Vomiting/ nausea	33 (20)	29 (21)	4 (14)	0.61
Vertigo	21 (13)	18 (13)	3 (11)	1.00
Other nonspecific symptoms	5 (3)	5 (4)	-	0.77
<i>Seizure</i>	30 (18)	27 (20)	3 (11)	0.42
Variables are expressed as n (%); p-values from χ^2 test or Fisher's exact test comparing symptoms of patients with RT and symptoms of patients with non-RT				
Presenting symptoms for the whole group (n=164) and divided by therapy.				

The time from symptom onset to confirmation of diagnosis was significantly shorter in the RT group than in the group without RT (mean 4.1h standard deviation (SD) 5.5 h vs. 20.4h SD 21.8, $p < 0.0001$) (see Fig. 1; log rank test $p < 0.0001$). Only in three patients, (age 4.1, 6.9 and 10.3 years) receiving RT diagnosis was confirmed after 6h (8h, 9.6h and 28h). These patients presented with mainly nonspecific symptoms such as headache, seizure and decreased consciousness. All three patients had a good neurological short-term outcome without any complications.

Cardiac disease as predisposing risk factor was present significantly more often in the recanalization group than in the non-recanalization group ($n = 14$, 50% vs $n = 33$, 24%; $p = 0.006$). The prothrombotic state was equally common in both groups ($n = 10$, 36% vs $n = 46$, 34%; $p = 0.85$), and arteriopathies were less commonly reported in the RT group ($n = 2$, 7% vs $n = 29$, 21%; $p = 0.08$).

Table 4 lists the affected vessels in both groups, showing that in the RT group, larger vessels, such as the middle cerebral artery (MCA) and internal carotid artery (ICA), were more often affected than in the non-RT group (statistically not significant). In all patients, thrombolysis was performed with recombinant tissue plasminogen activator (rt-PA). Dose information was obtained in 39% ($n = 11$) of patients. Analogous to adult stroke protocols, the standard dose was 0.9 mg/kg bodyweight. Two patients (both 15 years old) underwent local thrombolysis with an absolute rt-PA dose of 20 mg. Only in one patient (11.3-year-old girl) that underwent both thrombolysis and thrombectomy a minor bleed at the puncture site occurred as RT associated complication. No complications occurred in patients treated only with either thrombolysis or thrombectomy.

Table 4
AFFECTED VESSELS

Affected Vessel	All patients (n = 110)	No recanalization (n = 88)	thrombolysis (n = 7)	Thrombectomy (n = 8)	Lysis and Thrombectomy (n = 7)
Middle cerebral artery	75	57	6	6	6
Posterior cerebral artery	20	17	1	1	1
Anterior cerebral artery	15	15	–	-	-
Internal carotid artery	11	9	-	2	-
Cerebellar artery	5	5	-	-	-
Aa. lenticulostriatae	4	3	1	-	-
Basilar artery	2	1	-	-	1
Aa. thalamoperforantes	2	2	-	-	-
A. choroidea ant.	2	-	1	-	1
External carotid artery	1	1	-	-	-
Multiple affected vessel per patients (sum larger than total number)					
Affected vessels in the RT (n = 22) and non-RT groups (n = 88; data missing from 54 patients)					

The short-term outcome defined as residual neurological deficit at discharge was slightly worse in the recanalization group (statistically not significant). At discharge, 50% of the patients in the RT group had hemiparesis (vs. 40% in the non-recanalization group), 17% (vs. 14%) had facial palsy and 14% (vs. 11%) had speech disturbance (Table 1).

Antithrombotic therapy for secondary prophylaxis at discharge was performed in both groups with acetylsalicylic acid (ASA), low-molecular weight heparins (LMWH), vitamin K antagonists (VKAs) or a combination of ASA with other anticoagulants (not further specified). In the RT group ASA was more often used as single therapy for stroke prevention (9 (36%) vs 36 (26%; $p = 0.64$)) as well as in combination with other anticoagulants (7 (25%) vs 9 (7%); $p = 0.01$) and vitamin K antagonists (4 (14%) vs 2 (2%); $p = 0.01$)). LMWH was more often used in the non-recanalization group (55 (40%) vs 7 (25%) $p = 0.14$)).

Discussion

Acute ischemic stroke in childhood is a rare event but is associated with high clinical, psychological and economic burden due to neurological sequelae.[4, 29] Higher awareness among parents, paramedics and health care providers and better diagnostic and treatment modalities seem to have led to an increasing incidence over the last decades. In adults, emerging hyperacute therapies show overwhelming benefits in the treatment and outcome of stroke. Despite faster diagnoses of childhood AIS, prospective randomized pediatric trials are missing or have had to be stopped due to recruitment problems.[9, 10] Nevertheless, a series of observational data confirm the feasibility of thrombolysis and/or thrombectomy in CAIS.[9, 10, 12, 23, 24, 26, 30] The AHA Scientific Statement on the management of stroke in neonates and children as well as the Australian clinical consensus guideline state that the use of hyperacute recanalization treatment remains controversial and should still be limited to some children meeting adult eligibility criteria.[31, 32]

Moreover, comparing published pediatric stroke registry data from Amlie-Lefond et al.[12] (2% recanalization therapy in 4 years, 687 patients) and Bigi et al. [26] (11% RT in 15 years, 150 patients) with our data[28] (17% in 3 years, 164 patients), it seems that acute recanalization strategies have been increasingly used over the last years. As demonstrated in our study (88% diagnosed within the supposed critical time window of < 4.5 h), this might be explained by the

shorter time intervals from the onset of symptoms to diagnosis and therapy than those in the data published by Rafay et al. (22.7h median time interval).[7] Our data are in accordance with the median time intervals from the onset of symptoms to recanalization (4.0h) published by Sporns et al.[23] In the non-recanalization group, more than half of our patients (53%, n = 31) were diagnosed after 12h. The greater occurrence of symptoms such as speech disturbance, facial weakness and hemiparesis in the RT group might also trigger a faster diagnosis than for nonspecific symptoms.[28] Among patients older than five years, visual disturbances also occurred more often in the recanalization group. This might be associated with problems examining visual disturbances in children younger than five years of age. Three patients (age 4.1, 6.9 and 10.3 years) received recanalization therapy after the recommended time interval with a good short-term outcome. According to adult data from the Dawn and Defuse trial a larger therapy window might be supposed also for children and increase the number of patients eligible for RT.[20, 21]

More commonly appearing stroke symptoms such as hemiparesis, facial weakness or speech disturbance may explain the significantly higher incidence of thrombectomy in children older than five years. A comparable vessel size of MCA to adults in this patient group facilitates feasibility of RT.[33] Nevertheless, Sun et al. showed that RT might also be feasible in children between nine months and four years of age.[34] Our study adds three more patients below five years of age with successful RT without complications confirming the data from Sun et al.. Cardiac risk factors leading to cerebral thromboembolic vessel occlusion were significantly more represented in the recanalization group. Not surprisingly, embolic disease is a mainstay of RT. The incidence of prothrombotic state was similar in both groups, while arteriopathies were one of the most common risk factors for childhood AIS associated with a presumed higher interventional risk of bleeding. Relative contraindications such as arteriopathies, vasospasm or dissection were obviously underrepresented in the RT group.

The use of different antithrombotic therapies for secondary stroke prevention in our study reflects the recommendations to use either ASA or LMWH or VKA. The selection of respective therapies is triggered either by local standards or by additional risk factors for recurrence. The higher incidence of cardiac disease with the need of long-term antithrombotic therapy and adult standard of care after RT might explain the higher use of ASA and VKA for secondary prophylaxis in the RT subgroup.

In contrast to the Save ChildS Study[23] showing an improvement of the pediatric National Institutes of Health Stroke Scale (PedNIHSS) score with good short-term and long-term outcomes, we observed a slightly worse short-term outcome in the RT group. Possible causes for this difference may be the small number of patients and a selection bias for individuals being treated by the local treating pediatricians. Additionally, larger affected vessels and/or extension of the infarction area in the RT group could lead to worse outcome.

Strength and Limitations:

The strength of this subgroup analysis is the prospective design of this population-based study.[28] This real-world experience highlights relevant data on the current treatment practice and unmet needs of pediatric stroke care in Germany. The lack of a sufficient number of patients for performing meaningful statistics is a limitation of this study. As mentioned, underreporting to the ESPED may also be a significant limitation. Adult stroke units do not report adolescents with AIS to the ESPED. Reports from centers with higher pediatric stroke expertise might explain the low complication rates in this study group. Given the similarity to previously published data, it is unlikely that this underreporting might have influenced the results.[12, 23, 26] The study design (ESPED survey) without specifying standardized diagnostic and therapy protocols cannot provide further data on long-term outcomes.

Conclusion

The use of recanalization treatments in childhood AIS increased over recent years indicating increased earlier recognition of stroke and greater awareness of different treatment options. No increase of complication rates shows their feasibility and safety despite the restrictive recommendations of international pediatric stroke guidelines. The presence of predisposing risk factors such as arteriopathies and low levels of pediatric expertise make it difficult to extrapolate adult data. Pediatric stroke protocols and interdisciplinary treatments in pediatric stroke centers are necessary to identify eligible patients early as possible. Prospective studies on long-term outcomes are needed.

Methods

The 'Erhebungseinheit für seltene Pädiatrische Erkrankungen' (ESPED) is an established surveillance system for rare disorders in pediatrics. It requires anonymous reporting of rare disorders in childhood on a monthly basis from all German children's hospitals.[35] The case definition includes any patients with a first onset of CAIS between 28 days of life and 18 years, excluding (presumed) perinatal/neonatal stroke, hemorrhagic stroke and cerebral venous sinus thrombosis. The local treating physicians provided diagnostic modalities, diagnosis and therapy. A pseudonymized, standardized questionnaire was sent to the reporting clinician. Age, onset of symptoms, time span until diagnostic imaging and final diagnosis, imaging technique leading to diagnosis, risk factors and therapeutic strategies were queried (details in Gerstl et al).[28] All answer sheets were verified by a pediatric neurologist (LG) and pediatric hemostasis specialist (MO). Data were entered into a web-based database. This subgroup analysis investigates patients treated with intravenous/intraarterial thrombolysis and/or thrombectomy for hyperacute recanalization of affected vessels.

A description of patient's characteristics was obtained for the entire patient group and by type of treatment irrespective of missing values. Gerstl et al. showed that Pediatric NIH Stroke Scale (PedNIHSS) and the Pediatric Stroke Outcome Measure (PSOM) were barely used in Germany.[28] For this reason, in our subgroup analysis short-term outcome was defined as residual neurological symptoms at discharge. Statistical comparisons of patients with recanalization and patients without recanalization were performed using chi-squared or Fisher exact tests as appropriate. Investigations of the differences in time from the onset of symptoms until a confirmation of diagnosis was based on survival analysis using the product limit estimator. Statistical differences in the time to diagnosis were analyzed with the log-rank test. We used a significance level of 5% for all analyses without adjustment for multiple testing. All statistics were

calculated using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). All analyzed data involving human participants were in accordance with the ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics committee waived for informed consent from participants and/or their legal guardians to use patient data to guarantee anonymous incidence reporting of all German cases in accordance with the inclusion criteria and reporting of retrospective pseudonomized data to an independent ESPED data trustee. The data protection office and the ethics committee of the medical faculty of Ludwig-Maximilians University, Munich, approved the study (Nr 42 – 15; 05-04-2016).

Data availability statement:

Study protocol, statistical analyzes and anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with adherence to the legal requirements of Germany and the European Union legislation on the general data protection regulation.

Declarations

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Author contributions: MO reviewed answer sheets, performed statistical analysis, drafted the initial manuscript, and approved the final manuscript as submitted; ALS, RW performed statistical analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted; KK, CB, SJ, FH, KR, MB, MT, IB, FH, reviewed and revised the manuscript and approved the final manuscript as submitted; LG designed the study, reviewed answer sheets, reviewed and revised the manuscript, and approved the final manuscript as submitted

Statistical analysis: conducted by Anna-Lisa Sorg and Raphael Weinberger, Institute of Social Pediatrics and Adolescent Medicine, LMU Munich, Germany

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Figures

Figure 1

TIME FROM SYMPTOM ONSET TO DIAGNOSIS Comparison of the exact time (in h) from the symptom onset to confirmation of diagnosis in the non-RT (n=28) and RT groups (n=136).