Superselective Intra-arterial Thrombolysis for Acute Cardioembolic Stroke in a Child with Idiopathic Dilated Cardiomyopathy

A Case Report

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Summary

We describe a case of cardioembolic dominant hemisphere internal carotid artery occlusion in a child with idiopathic dilated cardiomyopathy. The patient was subjected to superselective local intra-arterial thrombolysis using recombinant tissue plasminogen activator (Alteplase; Actilyse®). In presence of good collateral flow local intra-arterial thrombolysis prevented a major dominant hemisphere ischaemic stroke, although post-interventional computed tomographic scans disclosed haemorrhagic conversion in the left corpus striatum. Forty eight months after ischaemic stroke and thrombolysis the patient is ambulatory with a moderate neurologic deficit.

Introduction

Acute ischaemic stroke (IS) is rare in children and young adults with an incidence of 1.2 to 2.5 cases per 100.000 per year [9,25,29,43,46]. Recent studies have indicated that 14% [25] to 65% [29] of childhood IS are cardioembolic in nature. In the setting of idiopathic dilated cardiomyopathy (IDCM) [1,2,8,15,30,45], left ventricular thrombus formation has been identified among the major risk sources of cardioembolic IS in both adult [6,22] and pediatric populations [17,23].

We describe a case of cardioembolic dominant hemisphere internal carotid artery (ICA) occlusion in a child with IDCM. The patient was subjected to superselective local intra-arterial thrombolysis (LIT) using recombinant tissue plasminogen activator (rTPA) (Alteplase; Actilyse (R), Boehringer Ingelheim, Germany). LIT in conjunction with good collateral flow prevented a major dominant hemisphere infarction.

Case Report

Clinical Presentation

A 2 9/12-year-old boy with IDCM presented with acute severe cardial insufficiency. Upon admission, dyspnea, pulmonary edema, foot edema, and hepatomegaly were apparent. Echocardiography disclosed thin layered dilated ventricles, decreased cardiac output, and a ventricular shortening fraction < 8%.

After administration of high dose furosemide, spironolactone, and continuous dopamine infusion the boy's condition improved. Despite low dose heparinization echocardiography after 24 hours demonstrated improved ventricular shortening fraction but by then a 19 mm left ventricular apical septum thrombus had appeared. Heparinization was

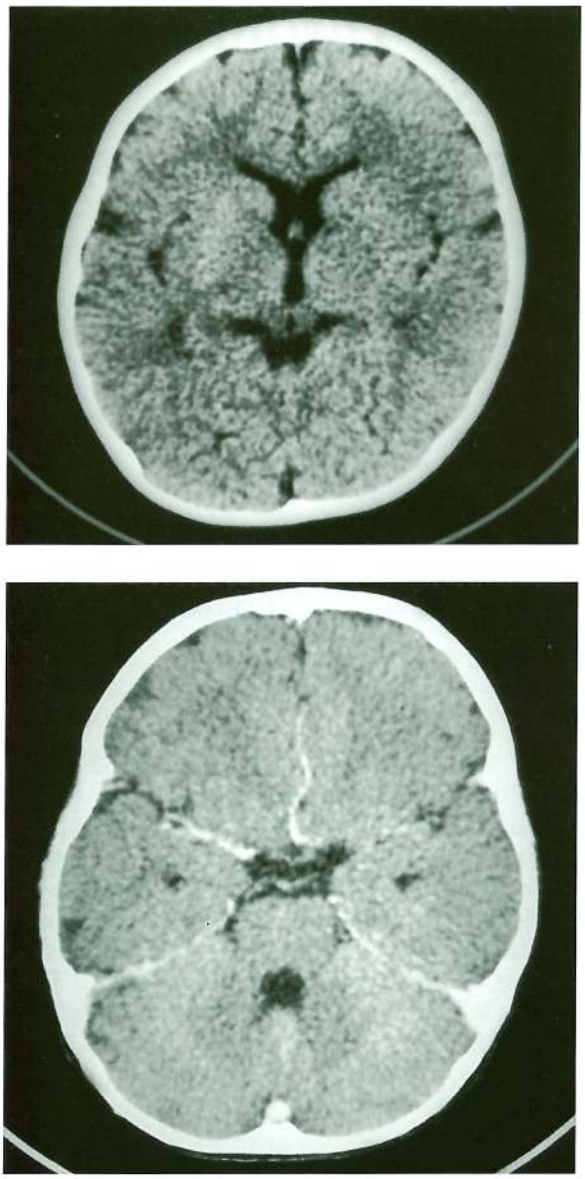

Figure 1 A) Computed tomographic scan, obtained within 2 hours of onset, failing to demonstrate early signs of acute infarction. B) Contrast-enhanced computed tomographic scan, obtained within 2 hours of onset, disclosing absence of left middle cerebral artery opacification.

therefore increased and echocardiography subsequently failed to demonstrate a change in thrombus size over the next three days. On day four, however, the boy became somnolent, tachycardic and presented a sudden onset right sided hemiparesis and facial nerve palsy. Echocardiography by then disclosed disappearance of the cardiac thrombus.

Computed tomographic (CT) scans obtained within one hour of onset failed to demonstrate early signs of acute cerebral ischaemia (figure 1A). Contrast-enhanced CT scans disclosed absence of left middle cerebral artery (MCA) opacification (figure 1B).

The rapid neurologic deterioration of the boy, disappearance of the cardiac thrombus, and absence of MCA opacification on CT scans indicated acute dominant hemisphere cardioembolic IS.

Intervention

Within 2.5 hours of onset the patient was taken to an interventional angiography suite to allow for diagnosis and LIT when indicated. The neurointerventional procedure was performed by one of the authours (A.G.). Angiography disclosed a left ICA occlusion in the C2 segment at the level of the posterior communicating artery (PCom) (figures 2A, 2B). Due to ICA occlusion the ipsilateral posterior cerebral artery (PCA) was strongly opacified via PCom cross flow. Right ICA injection demonstrated spontaneous filling of the left anterior cerebral artery (ACA) territory via the anterior communicating artery (ACom) and retrograde filling of the distal left MCA territory via leptomeningeal anastomoses. There was no opacification of the left MCA main stem or the lenticulostriate arteries either by spontaneous ACom cross flow or via leptomeningeal collateral flow, i.e. indicating both distal left ICA and proximal left MCA occlusion (i.e. "ICA T occlusion" [42,47]) (figure 2C). Vertebral artery angiograms demonstrated good filling of the right PCA, whereas the left PCA supplied from the left ICA via PCom cross flow was not opacified.

A guidewire controlled flow independent microcatheter with progressive softness (FasTracker 10; Boston Scientific/Target Therapeutics, Fremont CA, USA) was coaxially introduced through a 5F angiography catheter into the C2 segment of the left ICA. The microcatheter was advanced under roadmapping guidance to allow for superselective LIT (rTPA, 3 mg) with the single end-hole catheter tip embedded in the thrombus [10,14]. Left ICA angiograms obtained immediately thereafter disclosed repermeation of the ICA with filling of the left ACA territory but remanent thrombus in the left MCA main stem (figure

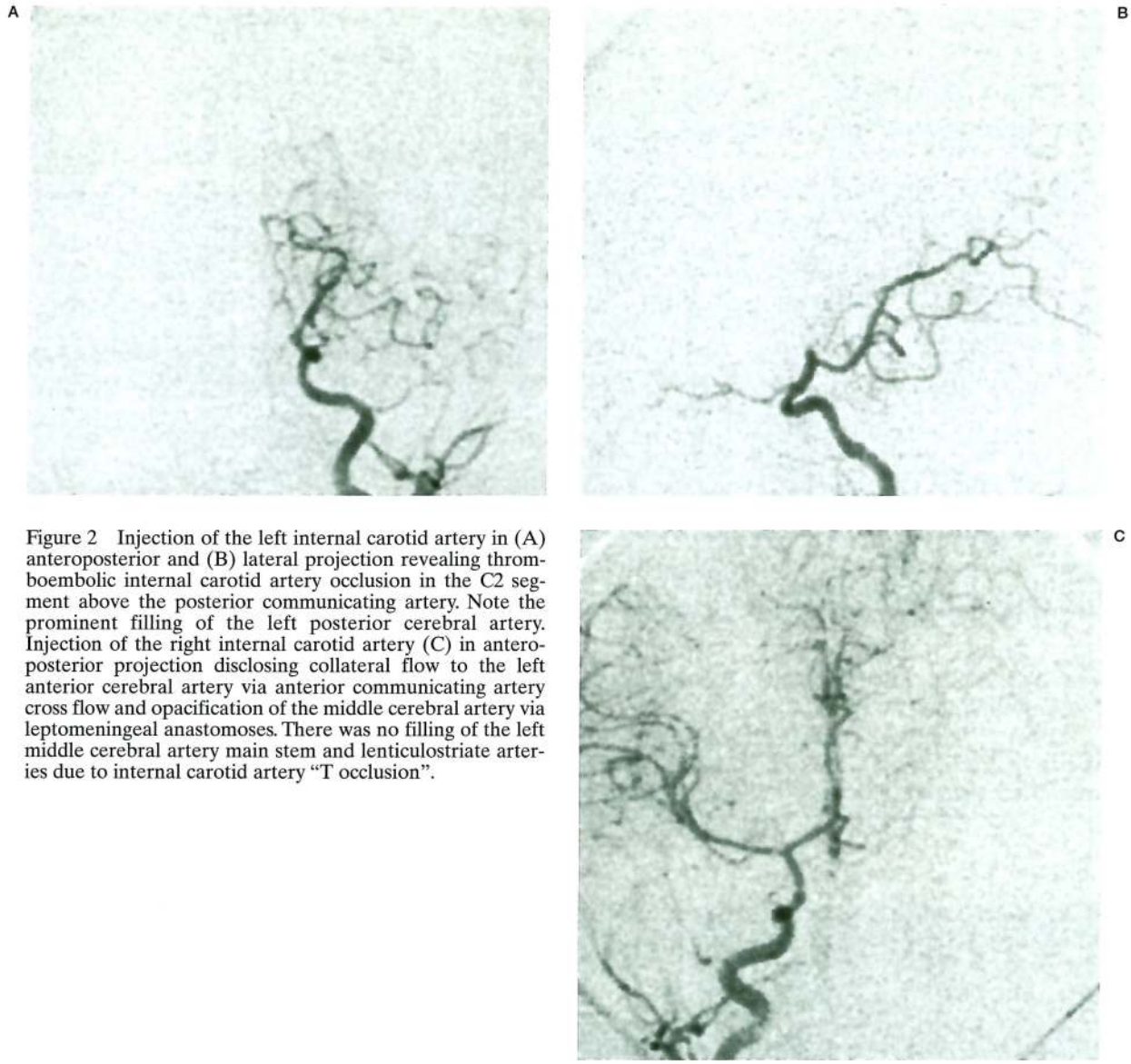

Figure 2 Injection of the left internal carotid artery in (A) anteroposterior and (B) lateral projection revealing thromboembolic internal carotid artery occlusion in the C2 segment above the posterior communicating artery. Note the prominent filling of the left posterior cerebral artery. Injection of the right internal carotid artery (C) in anteroposterior projection disclosing collateral flow to the left anterior cerebral artery via anterior communicating artery cross flow and opacification of the middle cerebral artery via leptomeningeal anastomoses. There was no filling of the left middle cerebral artery main stem and lenticulostriate arteries due to internal carotid artery "T occlusion".

3). The microcatheter was therefore further advanced and administration of 5 mg rTPA resulted in subtotal repermeation of the MCA territory. Since a residual thrombus had migrated to the left rolandic artery, superselective application of another 5 mg rTPA was required to attain repermeation of the rolandic branch (figure 4).

Left ICA angiograms thereafter demonstrated refilling of the entire left ACA and left MCA territory (figure 5). Heparinization was continued with the objective of achieving an activated partial thromboplastin time of twice the control value[24,27].

Clinical Course and Neurologic Outcome

After LIT the boy was transferred to the pediatric intensive care unit and could be extubated within four hours. The next morning he was transfered to the normal ward, where post-interventional CT scans disclosed haemorrhagic conversion in the left corpus striatum[11] but failed to demonstrate a major left hemispheric infarction (figure 6A).

Systemic heparinization was discontinued and digitalis, furosemide, spironolactone, and carnitine were administered to improve ventricular function. Four weeks after onset the boy

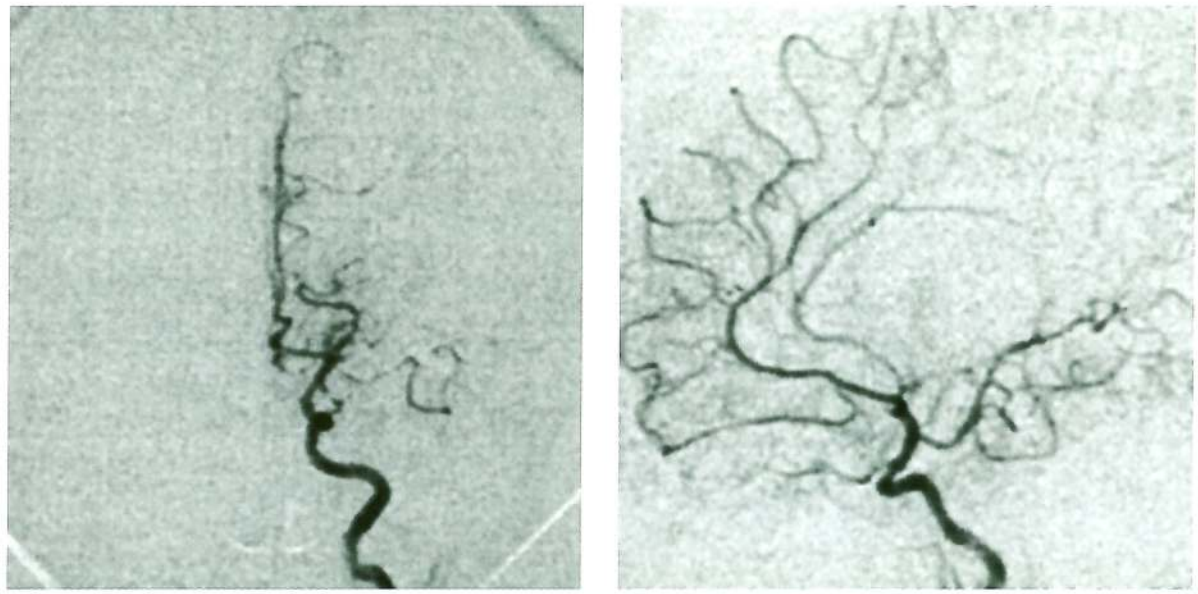

Figure 3 Angiograms in (A) anteroposterior and (B) lateral projection, obtained after local superselective thrombolysis (rTPA, 3 mg), disclosing repermeation of the left internal carotid artery with filling of the anterior cerebral artery territory and remanent thrombus in the middle cerebral artery main stem.

was dismissed with a right sided hemiparesis but ambulatory.

After six months ventricular function had improved to nearly normal. The origin of DCM remained unclear despite extensive investigations. CT scans obtained by then demonstrated a hypodensity in the left corpus striatum (figure 6B) resembling the area of post-thrombolysis haemorrhagic conversion. Upon 48-month follow-up examination, the patient was ambulatory with a spastic right sided hemiparesis in the absence of aphasia or psychomotor retardation.

Figure 4 Superselective angiogram in lateral projection after local superselective thrombolysis (rTPA, 5 mg) demonstrating repermeation of the left rolandic artery.

Discussion

Cerebral IS is rare in children and young adults. The incidence of childhood IS has been put at 1.2 to 2.5 cases per 100.000 per year [9,25,29,43,46]. Recent studies have indicated that childhood IS may be due to cardiogenic embolism in 14% [25] to 65% [29] of patients. Among the sources of cardiogenic embolism, IDCM [1,2,8,15,30,45] has been identified as a major risk source, since patients with depressed left ventricular systolic function are more prone to left ventricular thrombus formation.

Treatment options for cerebral IS include hypervolemic haemodilution [39], antithrombotic agents [24,27] and/or aspirin [40], cerebroprotective agents [31,36,37], and thrombolysis in selected cases [18,41]. Although spontaneous recanalization of occluded arteries has been described in 17% of cases [32], this event may often occur too late to be of clinical benefit.

Therefore, thrombolytic recanalization of the occluded cerebral vasculature holds promise as

a therapy for IS, provided that therapy can be accomplished soon after symptom onset, i.e. within a defined "therapeutic window". The relationship between duration and amount of reduced cerebral blood flow and the volume of cerebral infarction has been well established [38] and recent studies have indicated that thrombolytic measures may only be effective if started within six hours of IS [18], although the critical interval may be even shorter [7,19].

Recombinant TPA is a serine protease catalyzing the activation of plasminogen to plasmin. In humans and experimental animals, rTPA can induce a relatively clot-specific lysis of pathologic thrombi with only limited systemic plasminogen activation [3,21,48]. Systemic intravenous thrombolysis using rTPA increased the number of patients with good neurologic outcome in the National Institute of Neurologic Disorders and Stroke (NINDS) trial [41], whereas the European Cooperative Acute Stroke Study (ECASS) found improved neurologic outcomes only in defined subgroups [18].

Since local intra-arterial thrombolysis theoretically offers the advantage of selective drug delivery, a growing body of clinical studies has addressed this issue [4,10-14,16,20,35,42,44,47]. The recently published PROACT trial [12] demonstrated that LIT was associated with superior recanalization in thromboembolic IS when compared with placebo. Evidence is available indicating that LIT may be significantly more efficacious than intravenous thrombolysis as assessed by measures of angiographic vessel recanalization [12-16,35]. In the light of these findings we consider LIT – although not an established therapy for IS in any vascular territory – a reasonable therapeutic option for selected cases of acute IS when referred to medical centers with the infrastructure and the neurointerventional capabilities required to perform these procedures on an emergency basis.

The present case report found a benefit of LIT using rTPA in a 2 9/12-year-old boy with dominant hemisphere cardioembolic IS from IDCM. Superselective intra-arterial application of 13 mg rTPA (1mg/kg) resulted in recanalization of the occluded cerebral arteries with full return of perfusion in the dependent vascular territories, i.e. Mori recanalization grade 4 [32].

LIT was started within 2.5 hours of symptom onset. Pre-interventional CT scans failed to demonstrate areas of hypodensity in the left MCA territory indicative of early infarction [33]. Evidence is available indicating a positive correlation between the risk of intracerebral haemorrhage (ICH)/haemorrhagic conversion of ischaemic tissue and both 1) a prolonged interval from onset to lysis and 2) a higher dose of rTPA. Brott et Al [7] found a 4% incidence of ICH when patients were subjected to systemic thrombolysis within 90 minutes of IS, whereas

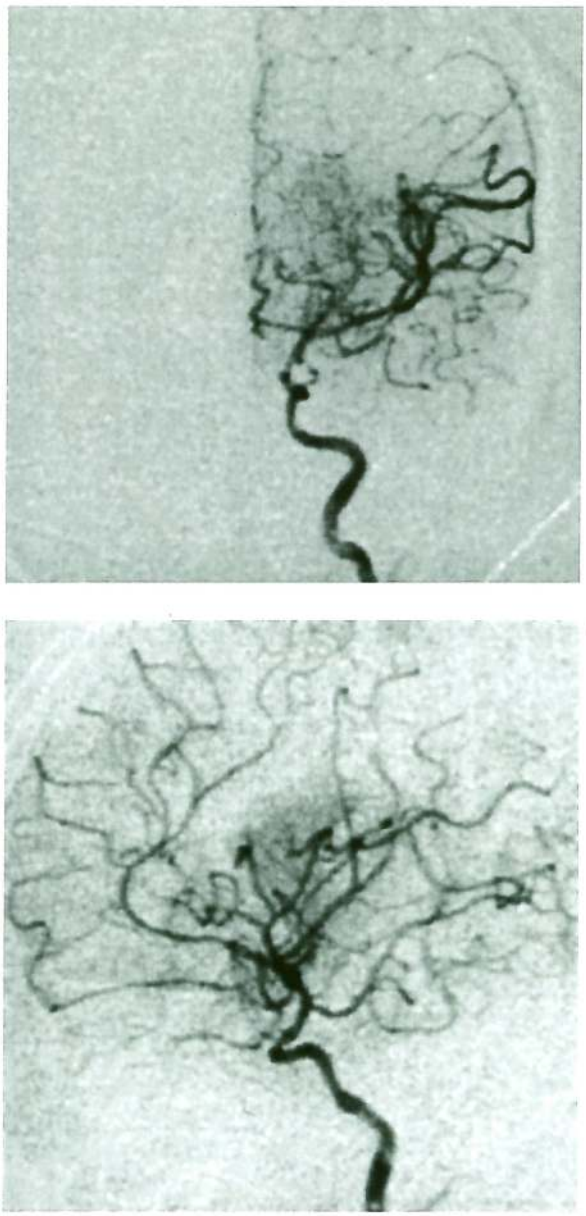

Figure 5 A) Anteroposterior and (B) lateral views of the left internal carotid artery after local superselective thrombolysis demonstrating sufficent repermeation.

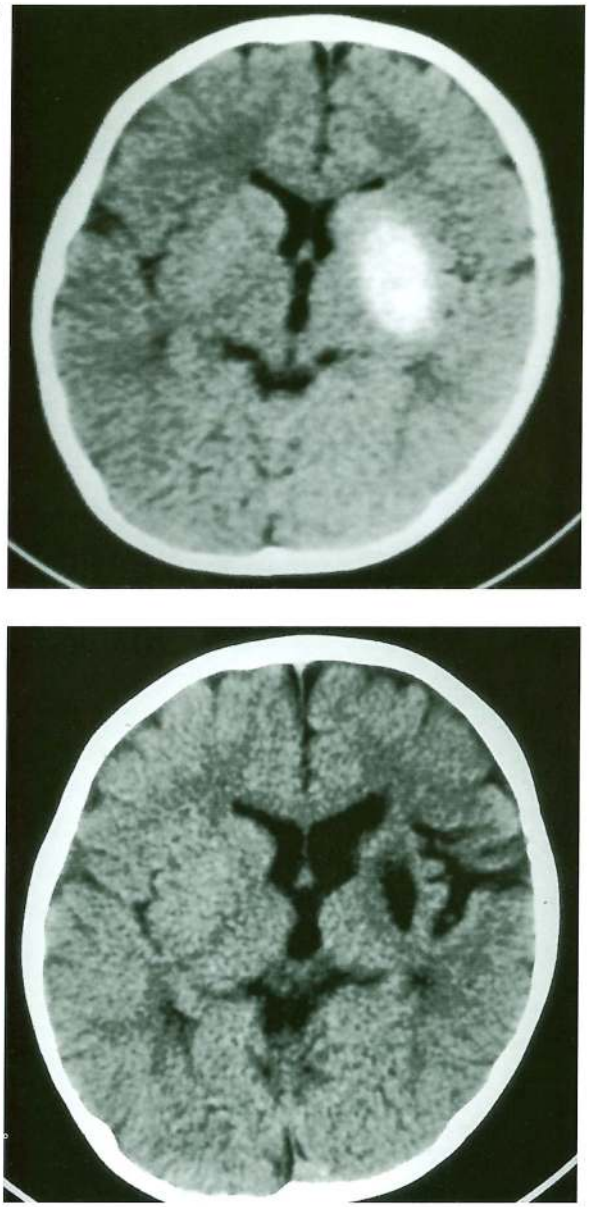

Figure 6 A) Post-interventional computed tomographic scans disclosing haemorrhagic conversion in the left corpus striatum but failing to demonstrate a major left hemispheric infarction. B) Follow-up computed tomographic scans, obtained 7 months after the procedure, demonstrating a hypodensity area in the left corpus striatum resembling the area of post-thrombolysis haemorrhagic conversion.

the ICH rate increased to 10% when patients were treated 91 to 180 minutes after onset [19]. The authors thereby demonstrated that ICH occurred only in patients treated with > 0.85 mg/kg rTPA [7]. In comparison, the NINDS trial including patients treated with 0.9 mg/kg rTPA i.v. within three hours of onset reported a 6.4% symptomatic ICH rate [41] and the ECASS including patients treated with 1.1 mg/kg rTPA i.v. within six hours of the ictus found a 6.3% ICH rate in the rTPA group [18]. Haemorrhagic conversion of ischaemic tissue, however, is a natural finding in embolic IS and the spontaneous haemorrhagic conversion rate following IS may reach 41% [34].

Although LIT was accomplished in a timely fashion, our patient suffered a haemorrhagic conversion in the corpus striatum of the affected hemisphere. Similarly, del Zoppo et Al [11] reported that all haemorrhagic complications encountered after LIT of acute carotid territory IS affected the ipsilateral corpus striatum. With regard to the interval between onset and therapy, the absence of hypodensity areas on CT scans suggested that LIT was attained within the therapeutic window recommended [33], although an even shorter interval would have been desirable [7,41]. With respect to thrombolytic therapy, it is reasonable to believe that the haemorrhagic conversion encountered in our case was related to the relatively high dose of rTPA applied during LIT (1 mg/kg) [7]. In detail, whereas 3 mg rTPA were required to repermeate the ICA and another 5 mg rTPA were sufficient to re-establish flow in the MCA main stem and lenticulostriate arteries, an additional 5 mg rTPA were necessitated to lyse the remaining thrombus which had migrated to the rolandic artery. Selective repermeation of this branch was considered indispensible since the migration of fragmented thrombus to a functional end artery will compromise regional cerebral blood flow more severely than does a more proximal occlusion.

Since the effects of heparinization in conjunction with thrombolytic therapy are not clear-cut, an association of early anticoagulation with the haemorrhagic complication encountered in our patient cannot be ruled out [24,27,40]. Systemic heparinization, however, was necessitated 1) in the presence of cardiac ventricular thrombus formation [26], 2) to prevent cardiogenic re-embolism in the setting of IDCM, and 3) to counteract post-thrombolytic re-occlusion of the left ICA/MCA [24].

The best predictor of good neurologic outcome appears to be the presence of good collateral flow, which presumably prolongs the viability of focally ischaemic tissue. Although pre-

treatment angiograms disclosed a good collateral circulation via 1) ACom cross flow and 2) leptomeningeal anastomoses, we believe that LIT was required in the present case. The absence of angiographic filling of the left MCA main stem indicated an "ICA T occlusion" [42,47]. In this setting, spontaneous collateral circulation would not have re-established arterial flow to the lenticulostriate arteries supplying the dominant hemisphere basal ganglia. The natural history of "ICA T occlusions" is grim. Zeumer et Al [47] reported a fatal outcome in 59% and severe permanent neurologic deficits in 38% of the patients treated. The recanalization rate of 17% was low. In light of these findings we made every effort to prevent a major dominant hemisphere IS and it is reasonable to believe that in the present case LIT ameliorated the natural course of the disease. Despite our efforts, however, the boy suffered a focal ischaemic lesion in the corpus striatum with subsequent haemorrhagic conversion [11].

Although LIT may be effective in achieving recanalization of occluded arteries with a 40% to 100% success rate in selected cases of IS [5], clinical outcome is unpredictable and often linked to the presence or absence of collateral flow [4,14] and the occurrence of haemorrhagic complications [11,18,41]. In the present case angiographic repermeation of the left ICA/MCA in presence of good collateral flow was paralleled by a moderate neurologic recovery upon 48 months clinical follow-up examination. This finding is in agreement with previous studies indicating that although 85% of children survive five years after onset of IS, residual deficits are apparent in 75%-100% of these patients [28].

Conclusion

The authors conclude that 1) superselective LIT is a useful therapeutic option for selected patients with acute IS and that 2) LIT may also be applicable in pediatric populations in the clinical setting of childhood cardioembolic stroke.

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