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Neonatal Cerebral Sinovenous Thrombosis: Neuroimaging and Long-term Follow-up

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Abstract

Neonates are known to have a higher risk of cerebral sinovenous thrombosis than children of other age groups. The exact incidence in neonates remains unknown and is likely to be underestimated, as clinical presentation is nonspecific and diagnosis can only be made when dedicated neuroimaging techniques, including computed tomographic venography or magnetic resonance venography, are performed. Associated intracranial lesions are common and some, such as a unilateral thalamic hemorrhage, should suggest cerebral sinovenous thrombosis as the underlying etiology. Neurodevelopmental outcome is poor in about 50% of these infants and is adversely affected by associated parenchymal lesions. Anticoagulation therapy will limit propagation of the clot and possibly the development or enhancement of parenchymal lesions. Multicenter randomized clinical trials are urgently needed to address many of these important issues.

Keywords

newborn; cerebral sinovenous thrombosis; MRI; hemorrhage; infarction

Introduction

Major advances in neuroimaging techniques have improved detection of cerebral sinovenous thrombosis in the newborn. The incidence in neonates is estimated at 1–12/100 000.^{1,2} This wide range is most likely due to differences in policy with regard to performing cranial ultrasound and especially magnetic resonance imaging (MRI), including magnetic resonance venography, in newborn infants admitted with neonatal seizures. Early detection also depends on the pattern of imaging abnormalities seen on initial imaging, which will be cranial ultrasound in most neonatal centers. In the presence of parenchymal abnormalities, such as a unilateral thalamic hemorrhage, cerebral sinovenous thrombosis is more likely to be considered in the differential diagnosis. In these infants, dedicated neuroimaging, including MRI and MR venography, will be performed and a diagnosis will be made. In the absence of parenchymal brain lesions, however, additional neuroimaging might not be performed, especially when neonatal seizures, the most common presenting symptom, are easy to control with a single antiepileptic drug.

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Recent data from the International Pediatric Stroke Study revealed that more than half (rather than a third as reported previously) of all cerebral sinovenous thromboses diagnosed during infancy through childhood occurred in newborn infants zero to 28 days old.^{3,4} In addition, males are significantly more often affected than females, a finding also reported by others.⁵⁻⁷ In this review, we describe the role of neuroimaging in the detection of cerebral sinovenous thrombosis and discuss factors that affect long-term neurodevelopmental outcome for these patients.

The Intracranial Venous System

The venous drainage of the brain consists of a network of veins and sinuses. The superficial venous system consists of the superior sagittal sinus, the transverse, torcular, and sigmoid sinuses, and the internal jugular veins. The superior sagittal sinus drains into the right lateral sinus and the jugular vein. The temporal and occipital (sub)cortex drain toward the transverse sinus, the rest toward the superior sagittal sinus, except for the central part of the convexity that drains into Sylvian veins and the cavernous sinus, and the central part of the mesial hemisphere that drains into either internal cerebral or basal vein. The deep venous system consists of the deep basal veins draining blood from basal ganglia (and germinal matrix area in preterm babies) into the paired internal cerebral veins, which join to form the vein of Galen and the straight sinus (Figure 1).

It has been suggested that cerebral sinovenous thrombosis more often involves the superficial system than the deep venous system. In a recent study, there was a good correlation between the site and the extent of sinovenous thrombosis and the location of brain lesions.⁸ The location of the thrombus itself may be hard to find. Eichler and colleagues only found evidence of an intraluminal clot on magnetic resonance venography in the deep venous system in 2 of 15 patients.⁹ In the remainder, a decreased flow-related enhancement within the dural venous sinuses was seen, associated with compression by adjacent subdural hematoma or sutural diastasis. They suggest that with evidence of sinovenous injury in the absence of identified thrombus, it is possible that clots dissolve quickly, escaping detection, or that the superficial venous system is vulnerable to mechanical forces during delivery.

In the study by deVeber,³ the superior sagittal sinus was reported to be most often involved, followed by the lateral sinus and the straight sinus. This was subsequently confirmed by others.^{3,7,10} It is well-established that about half of superior sagittal sinus thromboses are associated with transverse sinus thrombosis and about a third of sinovenous thromboses are associated with involvement of the deep venous system.¹¹ Involvement of the deep venous system can only be recognized with the use of phase contrast magnetic resonance angiography, 3-dimensional magnetic resonance venography, or computed tomographic venography (Figure 2). One potential pitfall of magnetic resonance venography in neonates is that there is a high proportion of flow gaps in the venous sinuses, particularly the posterior aspect of the superior sagittal sinus, which could be attributed to the age-related smaller caliber of the sinus, smaller venous flow, and skull molding.¹² The apparent lack of flow across one transverse sinus can be due to the fact that the sinus is coplanar with the imaging plane. The use of quantitative flow values may help to confirm or discard a transverse sinus thrombosis. Quantitative flow values can be calculated with phase contrast magnetic resonance angiography in each vessel by integrating velocities across manually drawn regions of interest that closely enclosed the vessel lumen.¹³ In our own series, we found involvement of the straight sinus (87%) to be more common than involvement of the superior sagittal sinus (62%). This was often, as expected from the venous drainage system, associated with a unilateral thalamic hemorrhage (Figure 3).^{14,15}

Comparison with Literature

A systematic literature search was performed in PubMed, EMBASE, and Cochrane databases. In the search strategy, synonyms for 'cerebral sinovenous thrombosis' and synonyms for 'neonates' were combined. All papers describing neuroimaging in cohorts of neonates with cerebral sinovenous thrombosis were included. Papers that described a mixed population of neonates and older children were only included when it was possible to extract the neonatal data. Data regarding diagnostic imaging were gathered from the included studies (Table 1).

Computed tomographic venography is still frequently used to confirm a diagnosis of cerebral sinovenous thrombosis. In several studies, both CT and MRI were used in the diagnostic process. A disadvantage of CT/CT venography is the use of ionizing radiation and the need for intravenous administration of a contrast agent with a small risk of an allergic reaction, (transient) hypothyroidism, or contrast nephropathy.^{16,17} However, when magnetic resonance imaging is not available or possible at the early stages of admission, CT venography or multidetector computed tomographic venogram can be very useful in confirming the diagnosis of cerebral sinovenous thrombosis.^{18,19} Early imaging is of the utmost importance, since in some infants recanalization can be fast; if no adequate imaging is performed early, the diagnosis may be missed. In our own cohort, the diagnosis of cerebral sinovenous thrombosis could not be confirmed in 6 infants although the associated lesions were strongly suggestive of the diagnosis. It is important to make a correct diagnosis, since some of these infants have an underlying prothrombotic disorder and may be at risk for recurrent thrombosis.²⁰

For the associated lesions, the differences in percentages between the studies are likely to be partly the result of differences in exact terminology. In most studies, no distinction between hemorrhagic and ischemic infarction was made. The same applies for the general term 'hemorrhage' without differentiating between intraventricular or parenchymal hemorrhage and/or punctate white matter lesions. In general, associated lesions are seen in most of these infants; Grunt and colleagues found this to be significantly more common in neonates than in children ($P < .001$).⁷ Infants with associated parenchymal lesions are likely to represent the more severe end of the spectrum and the associated lesions are quite often the reason to perform further imaging. It remains likely, therefore, that less severe cases of cerebral sinovenous thrombosis are missed, since presentation is nonspecific.

Typical Neuroimaging Findings

Cerebral sinovenous thrombosis can be suggested by the presence of typical intracranial lesions, often first detected on cranial ultrasound. The presence of an intraventricular hemorrhage in a full-term infant—especially in association with a unilateral thalamic hemorrhage, which is easy to detect with cranial ultrasound—should raise strong suspicion for cerebral sinovenous thrombosis.^{14,21} Wu and colleagues noted that compared with newborns who only had an intraventricular hemorrhage (5 of 21), full-term infants who also had a unilateral thalamic hemorrhage (4 of 5) were significantly more likely to have sinovenous thrombosis. These findings tend to be associated with periventricular congestion, and these changes in the white matter follow the medullary veins and are usually more prominent in the frontal white matter. Other intracranial lesions, such as the so-called 'red infarcts,' are often located in the parietal region and will easily be missed using cranial ultrasound. In the preterm infant, cerebral sinovenous thrombosis should be considered when there is bilateral white matter involvement, often associated with an intraventricular hemorrhage with an unexpected late onset following an otherwise uncomplicated neonatal course.^{15,22}

In some cases, Doppler flow ultrasonography may demonstrate absent or decreased flow in the affected sinus and this can further support a probable diagnosis. In the study by Grunt and colleagues, 48% of cerebral sinovenous thromboses were detected with power Doppler ultrasound.⁷ At present, however, Doppler flow ultrasonography is not routinely performed in all infants admitted to a neonatal intensive care unit and might only be performed when a typical intracranial lesion, such as a thalamic hemorrhage, does suggest the presence of a cerebral sinovenous thrombosis. In the absence of intracranial lesions, magnetic resonance venography or computed tomographic venography are essential to making the diagnosis. We therefore recommend using magnetic resonance venography routinely in all infants with neonatal seizures who undergo an magnetic resonance examination.

Clinical Presentation in Relation to Imaging Findings

Clinical presentation has previously been described in cohorts of predominantly full-term infants. In the 2 largest studies reported so far, seizures and/or apneas were the presenting symptoms in about 75% of the infants.^{2,10} In the study by Berfelo and colleagues, a distinction was made between generalized and focal seizures, with generalized seizures being more common. Apneas were the presenting symptom in 17 and 19% of cases, respectively, and could well have been of epileptic origin, but this could not be confirmed due to the lack of continuous electroencephalographic monitoring. It has recently been suggested that infants with temporal lobe hemorrhage and possible involvement of the vein of Labbé tend to present with apneic spells.^{23,24} As expected, seizures were almost invariably present in the context of parenchymal lesions (38 of the 42 infants).² Cerebral sinovenous thrombosis can also be a chance finding (5% to 13%), diagnosed on a routine cranial ultrasound. It is therefore likely that cerebral sinovenous thrombosis is more common than reported.^{2,10,25}

Neurodevelopmental Outcome

Data on neurodevelopmental outcome will very much depend on the threshold of performing neuroimaging with the routine use of magnetic resonance venography. If only those infants with parenchymal lesions on initial cranial ultrasound will have computed tomographic venography or magnetic resonance venography, then the outcome data are likely to be worse. Fitzgerald and colleagues found a significant association ($P = .03$) between infarction and impairment at follow-up.¹⁰ Mortality and redirection of care will also affect subsequent outcome data. Mortality varies between 2% and 19%.^{2,4,10} As in any other group with perinatally acquired problems, cognitive deficits in these infants will likely only become clear once they reach school age. Age at follow-up is often not clearly stated and tends to show a wide range, but most outcome data are obtained at a median age of 24 months.^{2,4} Previous cohort studies found moderate to severe impairments in 40% to 45% of the survivors,^{2,3,4,10} as shown in Table 2. Postneonatal epilepsy was noted to occur in 16% to 41% of the children.^{2,10} Development of postneonatal epilepsy may also occur later in a subgroup of infants. Hypsarrhythmia has been reported in infants with cerebral sinovenous thrombosis.²⁶

Infants from our own population were born between March 2002 and April 2010. We were able to diagnose cerebral sinovenous thrombosis in 33 infants (8 preterm and 25 full-term) who were admitted to our Level 3 neonatal intensive care unit at Wilhelmina Children's Hospital in Utrecht. Every infant had a cranial ultrasound examination on admission and every infant who had neonatal seizures as a presenting symptom or develops neonatal seizures during the admission period had an MRI/magnetic resonance venography examination. All neonates had at least one MRI/magnetic resonance venogram within the first week after admission to confirm the diagnosis of cerebral sinovenous thrombosis. A

diagnosis of occlusion of the superior sagittal sinus and the straight sinus could be made in 26 infants when magnetic resonance venography and/or 2-dimensional phase contrast magnetic resonance angiography sagittal images showed clear lack of flow in a sinus at a threshold of 300 and 150 mm/s in combination with signal abnormalities suggestive for thrombosis on T1-weighted and T2-weighted images.¹⁹

Since 2008 onward, 3-dimensional magnetic resonance venography became available (Repetition time (TR), 18 ms; Echo time (TE), 6.6 ms; voxel size, 0.8 mm; Phase contrast (PC), 150 mm/s; scan time, 234 s). Three-dimensional magnetic resonance venography allows better visualization of the deep venous system. Three-dimensional magnetic resonance venography is already possible in very low birth weight infants, while phase contrast magnetic resonance angiography gives less reliable results due to the low flow velocity in these infants, and it is sometimes not successful in the preterm infant (Figure 4). From 3-dimensional magnetic resonance venography, maximum intensity projections are reconstructed using the system software. In our study, the magnetic resonance investigations were performed on a 1.5 Tesla ACS-NT system or a 3.0 Tesla whole-body Achieva system (Philips Medical Systems, Best, the Netherlands). At 3 months of age, a follow-up MRI was always performed to assess recanalization. In a small subgroup of infants, a third MRI was performed later in infancy or childhood.

Clinical Presentation

In agreement with previous studies, focal or generalized seizures were the most common presenting symptom in the 25 infants who were full-term, but 5 (20%) of the infants presented with respiratory insufficiency and/or perinatal asphyxia. The diagnosis of cerebral sinovenous thrombosis was only suspected on cranial ultrasound in one of these 5 infants who showed a unilateral thalamic hemorrhage, while the diagnosis was first made on magnetic resonance venography in the other 4 infants (Figure 5).

We were able to diagnose cerebral sinovenous thrombosis in both preterm as well as full-term infants, in contrast to most previous studies. Clinical presentation in the preterm infant was variable and related to a meningitis in 3 of 8 infants (Proteus, Listeria, Group B Streptococcus) and to dehydration in 3 infants with onset of symptoms between day 6 and 29.³⁰ In one infant, cerebral sinovenous thrombosis was a chance finding based on a routine cranial ultrasound performed on admission, showing a large intraventricular hemorrhage associated with an ipsilateral thalamic hemorrhage. In the remaining infant, late-onset white matter changes were seen on cranial ultrasound, and except for a factor V Leiden mutation, no other underlying problems were present.

Neuroimaging Findings

The pattern of intracranial lesions in the 25 full-term infants we studied was in agreement with previously published data, although the number of infants¹³ with a unilateral thalamic hemorrhage was larger than reported previously.^{3,10} The straight sinus was therefore the most commonly affected sinus, which we were unable to explain.

The pattern of associated intracranial lesions in the 8 preterm infants differed from the pattern seen in the full-term infants. Predominant and extensive white matter involvement was seen in all but one of the infants and these infants were initially stable. The lesions in the white matter were not dissimilar from cystic periventricular leukomalacia. However, when looking at the data in more detail, presentation was unusual in that it was beyond the immediate neonatal period and was associated with an intraventricular hemorrhage. The diagnosis of cerebral sinovenous thrombosis, however, would have been missed if magnetic resonance venography had not been performed. On 3-dimensional magnetic resonance

venography, the superior sagittal sinus was involved in all but one of the infants, with additional occlusion of either the straight sinus or the transverse sinus in all (Figure 6).

Subsequent Outcome

In our own cohort, age at follow-up of the 20 survivors with a cerebral sinovenous thrombosis confirmed by MRI-magnetic resonance venography ranges from 6 to 70 months. Twelve children have now been seen at 2 years of age or above. Of these 12 children, 3 have a developmental quotient on the Griffiths Mental Developmental Scale³¹ below -1 standard deviation; the mean developmental quotient was 89 with and 94 without including the children with a developmental quotient below -1 standard deviation. One preterm infant developed severe psychomotor retardation and epilepsy; he was too severely affected for us to be able to calculate a developmental quotient. Four children have now been seen between 3 and 7 years of age and a decline in their performance was noted in 3.

Of the total group of 20 survivors, 4 (19%) have developed epilepsy to date (one preterm, 3 full-term). A fifth child had several convulsions during periods of fever but has now been seizure-free without medication for more than 3 years. Postnatal epilepsy in the full-term infants first occurred at ages ranging between 2 and 7 years. None of the full-term infants developed cerebral palsy. Two children developed a very mild hand preference but were able to use both hands. These outcome data are better than reported previously^{4,7,10} It is of great interest that in the multivariate analysis of the study of Grunt and colleagues, absence of anticoagulant therapy was noted to be an independent risk factor of poor outcome. Our policy is to use anticoagulant therapy in all full-term infants, even in the presence of a parenchymal hemorrhage. Although our numbers are still too small to draw any conclusions, one could speculate that the use of anticoagulant therapy had a positive effect on neurodevelopmental outcome.¹⁴ The use of anticoagulant therapy in the presence of a parenchymal hemorrhage is, however, not recommended.^{4,32}

We have previously reported that our preterm population had a worse outcome,¹⁵ with neonatal death after withdrawal of intensive care treatment in 5 infants and severe psychomotor retardation and epilepsy in 2 of the 3 survivors. Only one preterm infant, with late-onset white matter changes, has a mildly abnormal outcome (delayed neurodevelopment and strabismus) at 15 months.

Conclusions

Cerebral sinovenous thrombosis is a serious condition in neonates that often goes unrecognized because of its nonspecific presentation. Early neuroimaging, including the routine use of magnetic resonance venography in all infants with neonatal seizures, will improve detection. As we demonstrated, this is possible in both preterm and full-term infants.

When cerebral sinovenous thrombosis is correctly diagnosed, anticoagulant therapy can be considered. Although the risks and effectiveness of anticoagulant therapy in neonates with cerebral sinovenous thrombosis has not yet been fully determined, preliminary results do suggest a better outcome in infants treated with anticoagulation compared with those who were not treated. However, more long-term follow-up data using strict and predefined protocols are needed to assess neurodevelopmental outcome at school age in this population.

With the increasing amount of research into cerebral sinovenous thrombosis, numerous questions are raised about this condition that cannot be answered by one center alone. Multicenter randomized trials are, therefore, urgently needed to answer many of these important questions.

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Figure 2.

Comparison of a 2-dimensional phase contrast (a) and a 3-dimensional MR venogram (b) in a full-term infant with thrombosis of the straight sinus. Although the lack of flow was seen on the 2-dimensional phase contrast angiography, more information is obtained with the 3-dimensional MR venogram, which also shows preservation of the anterior part of the superior sagittal sinus.

Figure 3.

Cranial ultrasound in a full-term infant presenting with seizures following dehydration, showing a large thalamic hemorrhage in the coronal (a) and sagittal (b) view. The associated intraventricular hemorrhage is best seen in the parasagittal view. The MRI, performed the day after admission, (c) shows a small intraventricular hemorrhage and a large left-sided thalamic hemorrhage. Also note the punctate lesions in the frontal white matter seen as low-signal-intensity lesions on this T2-weighted spin-echo image. A repeat MRI at 3 months (d) (inversion recovery sequence) shows partial resolution of the hemorrhage and mild ex-vacuo dilatation of the left ventricle. The 3-dimensional MR venogram on admission (e) shows lack of flow across the superior sagittal sinus and straight sinus, which has resolved 3 months later (f).

Figure 4. Three-dimensional MR venogram in a preterm infant with a weight of 1030 grams (a) and a full-term infant (b). MR venography was performed routinely and no cerebral sinovenous thrombosis was present.

Figure 5.

Full-term infant with perinatal asphyxia and neonatal seizures. Lack of flow in the superior sagittal sinus using cranial ultrasound. MRI shows no flow void and a very dilated sinus on the T2-weighted spin-echo image (a). The mid-sagittal T1-weighted image shows a severely dilated superior sagittal sinus without flow; this is also seen on the 2-dimensional Phase contrast angiography. Outcome was normal at 24 months (developmental quotient, 102).

Figure 6.

Preterm infant (gestational age, 30 weeks) with a *Listeria monocytogenes* infection. Cranial ultrasound on Day 1 shows inhomogeneous echogenicity in the periventricular white matter and blood in the ventricles (a). MRI performed on Day 4 confirms the cranial ultrasound findings and also shows lack of flow void in the superior sagittal sinus (b). Diffusion-weighted image shows extensive involvement of the white matter (c). Cerebral sinovenous thrombosis of the superior sagittal sinus and straight sinus were confirmed at postmortem examination.

Table 1

Imaging Methods and Findings in Several Cohorts of Neonates with CSVT

Author, Year	No of Patients*	No Preterm/ No Term	Imaging Method		Sinuses Involved			Associated Lesions						
			CT	MRI	MRV	SSS	Str	Tra	Mul	Inf	IVH	PWML	Thal	PVL
deVeber, 2001	69	0/69	-	-	-	43 (62%)	21 (30%)	27 (39%)	-	29 (42%)	-	-	-	-
Moharir, 2010	83	-	-	-	-	-	-	-	68 (82%)	29 (35%)	25 (30%)	-	-	-
Wu, 2005	30	1/29	3	27	-	-	-	-	-	15 (50%)	10 (33%)	-	5 (17%)	-
Fitzgerald, 2006	42	6/36	3	36	18	28 (67%)	14 (33%)	23 (55%)	21 (50%)	25 (60%)	8 (19%)	-	-	-
Nwosu, 2008	59	12/47	48	55	10	44 (75%)	18 (31%)	37 (63%)	42 (71%)	32 (54%)	11 (19%)	-	-	7 (12%)
Eichler, 2007	15	1/14	15	15	14	-	1 (7%)	-	-	-	4 (27%)	-	2 (13%)	-
Wasay, 2008	25	-	18	10	10	-	-	-	-	-	-	-	-	-
Teksam, 2008	34	-	22	15	15	14 (41%)	12 (35%)	24 (71%)	-	-	-	-	3 (9%)	-
Jordan, 2010	84	0/84	3	81	56	-	-	-	-	-	-	-	-	-
Grunt, 2010	21	4/17	4	20	7	17 (81%)	13 (62%)	9 (43%)	16 (76%)	10 (48%)	8 (38%)	-	7 (33%)	-
Berfelo, 2010	52	5/47	0	52	52	13 ^A	8 ^A	3 ^A	26 (50%)	41 (79%)	29 (56%)	-	25 (48%)	-
Kersbergen, 2011	26	6/20	0	26	26	17 (65%)	22 (85%)	10 (38%)	21 (81%)	7 (27%)	20 (77%)	15 (58%)	13 (50%)	6 (23%)

Abbreviations: CSVT, cerebral sinovenous thrombosis; Inf, infarction; IVH, intraventricular hemorrhage; mul, multiple sinuses involved; PVL, periventricular leukomalacia; PWML, punctate white matter lesions; SSS, superior sagittal sinus; st, straight sinus; Thal, thalamic hemorrhage; tra, transverse sinus.

* Only neonatal cases included

^A In these numbers, patients with occlusion of multiple sinuses were not included.

Part of the population in the study of Moharir was previously reported on in the study of deVeber. The same applies for the studies of Nwosu and Fitzgerald, and the studies of Kersbergen and Berfelo.

Table 2

Neurodevelopmental Follow-up in Several Cohorts of Neonates with CSVT

Author, Year	No of Patients*	No Preterm/ No Term	Treatment	Problems During Neurodevelopmental Follow-up		
				Cognitive	Motor	Epilepsy
deVeber, 2001	69	0/69	25	(36%)	-	12 (17%)
Moharir, 2010	83	-	38	(46%)	33 [^] (40%)	-
Wu, 2005	30	1/29	-	-	-	-
Fitzgerald, 2006	42	6/36	3	(7%)	16/27 (60%)	11/27 (41%)
Nwosu, 2008	59	12/47	-	-	-	-
Eichler, 2007	15	1/14	-	-	-	-
Wasay, 2008	25	-	-	-	-	-
Teksam, 2008	34	-	-	-	-	-
Jordan, 2010	84	0/84	43/81	(53%)	-	-
Grunt, 2010	21	4/17	7	(33%)	8/13 (62%)	5/13 (38%)
Berfelo, 2010	52	5/47	22	(42%)	20/39 [#] (51%)	9 (17%)
Kersbergen, 2011	26	6/20	16	(62%)	5/20 (25%)	3/20 (15%)

Abbreviations: CSV T, cerebral sinovenous thrombosis; PSOM, Pediatric Stroke Outcome Measure.

[^] Using the PSOM Scale, no detailed information given.

[#] Outcome only described as moderately or severely abnormal, no detailed information given.

Treatment = any form of anticoagulant use (e.g., low molecular weight heparin). Problems during neurodevelopmental follow-up = any form of impairment, no differentiation in severity. Part of the population in the study of Moharir was previously reported on in the study of deVeber. The same applies for the studies of Nwosu and Fitzgerald, and the studies of Kersbergen and Berfelo.