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Cardiac and Neurologic Outcome of Cardiac Rhabdomyoma considerations for prenatal counseling

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Sabrina DEGUELDRE

Médecin diplômée de la Confédération Suisse
Originaire de Brugg (AG) et de Belgique

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Cardiac and neurologic outcome of cardiac rhabdomyoma considerations for prenatal counseling

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Résumé

Les rhabdomyomes cardiaques sont des tumeurs cardiaques bénignes avec toutefois des complications cardiaques possibles et surtout avec une association pour la sclérose tubéreuse de Bourneville qui détermine le pronostic neurologique.

Cette étude présente une analyse du suivi cardiologique et neurologique à long terme d'enfants avec un diagnostic de rhabdomyomes cardiaques dans le but de mieux informer les parents lors de la consultation anténatale.

L'ensemble des cas de rhabdomyomes cardiaques diagnostiqués au moyen de l'échocardiographie pendant la période anténatale ainsi que postnatale a été répertorié d'août 1982 à septembre 2007. Des facteurs indépendants, tels que le nombre et la localisation des tumeurs, ont été analysés pour leur association avec le diagnostic de la sclérose tubéreuse de Bourneville, afin de prédire le pronostic cardiaque et neurologique de ces patients.

Les complications cardiaques retrouvées sont les arythmies, les obstructions des voies d'éjection ventriculaire et le choc cardiogène secondaire. Les arythmies sont les problèmes les plus fréquemment rencontrés pendant la période néonatale. La tachycardie supraventriculaire est le trouble de rythme le plus souvent identifié. Néanmoins, il n'y a pas de dimension ou de localisation spécifique d'un rhabdomyome cardiaque qui pourrait prédire ces troubles du rythme.

L'importance de l'association au diagnostic de la sclérose tubéreuse de Bourneville chez les patients atteints de rhabdomyomes est démontrée à travers les complications du développement neurologique avec une atteinte épileptique dans 80% des cas ainsi qu'un retard de développement dans 63% des cas.

La présence de multiples tumeurs cardiaques chez un patient suggère un risque accru d'être atteint de la sclérose tubéreuse de Bourneville comparé à un patient atteint d'une tumeur unique.

Les rhabdomyomes cardiaques régressent après la naissance et après la période périnatale les complications cardiaques deviennent rares. Toutefois, l'association à la sclérose tubéreuse de Bourneville domine le tableau clinique avec des complications au niveau du développement neurologique et forme donc un aspect important lors de la consultation anténatale.

Abstract

Cardiac rhabdomyomas are benign cardiac tumors with few cardiac complications but with a known association to tuberous sclerosis that affects the neurologic outcome of the patients.

This study analyses the long-term cardiac and neurological outcome of patients with cardiac rhabdomyomas in order to allow comprehensive prenatal counseling.

All prenatal and postnatal cases with echocardiographic diagnosis of cardiac rhabdomyomas encountered from August 1982 - September 2007 have been recorded. Independent factors, such as the number and the location of the tumors, have been analyzed for association with a diagnosis of tuberous sclerosis, in order to predict the cardiac and neurologic outcome of the patients.

Cardiac complications include arrhythmias, outflow tract obstruction, secondary cardiogenic shock. Arrhythmias are the most often encountered problems during the neonatal period. Supraventricular tachycardia is the commonest rhythm disturbance identified. However, no specific dimension or location of the cardiac rhabdomyomas may predict the rhythm disturbances.

The importance of the diagnosis of tuberous sclerosis in patients presenting with cardiac rhabdomyomas is exemplified by the neurodevelopmental complications showing 80% of cases with epilepsy and 63% of cases with a delayed development.

The presence of multiple cardiac tumors in patients suggests a higher risk to be affected by tuberous sclerosis, compared to patients with a single tumor.

Cardiac rhabdomyomas generally regress after birth and after the perinatal period cardiac-related problems are rare, but tuberous sclerosis and the associated neurodevelopmental complications dominate the clinical picture and should form an important aspect of the prenatal counseling of parents.

1. Introduction

The diagnosis of cardiac rhabdomyomas can either be prenatal, as an incidental finding in the fetal cardiology clinic or may be a finding in the postnatal work-up for tuberous sclerosis. Cardiac tumors are rare, the incidence of the primary tumors of the heart and pericardium, reported from autopsy studies of patients of all ages, varies from 0.17 to 28 in 10'000[i]. In children, the most frequent histological types are rhabdomyomas (60%), teratomas (25%) and fibromas (12%). The in-utero course depends on the growth and on the size of the tumors. Large masses can cause hemodynamic obstruction and subsequent heart failure, as well as fetal hydrops or tachyarrhythmia.[2-7] While these life threatening complications in the perinatal period are relatively rare, cardiac complications such as rhythm disturbances as well as the association with tuberous sclerosis[8] represent the crucial point for the long-term outcome.[9] Cardiac rhabdomyomas are reported to be associated with tuberous sclerosis in approximately 50% to 86% of patients [10, 11] and up to 80% of patients with tuberous sclerosis have cardiac rhabdomyomas.[12] Therefore, the association to tuberous sclerosis should form an important issue during the prenatal counseling of parents. The aim of this study is to analyze the data of patients with cardiac rhabdomyomas and their long-term cardiac and neurological outcome in order to allow comprehensive prenatal counseling.

2. Methods

This multi-center retrospective study was performed on the data of all patients with echocardiographic diagnosis of cardiac rhabdomyoma encountered at our institutions from August 1982 to September 2007. The criteria for the diagnosis of rhabdomyomas included the demonstration of the presence of multiple intracardiac tumors with characteristic echocardiographic appearance, in the absence of known malignant disease or existence of one or more tumors in association with tuberous sclerosis. These criteria were based on the information that fibromas and myxomas are invariably solitary tumors and on the very strong association between rhabdomyomas and tuberous sclerosis. A further and most important criterion was the evolution of the tumors, which is their tendency to regress and disappear in time.
The patients with a prenatal diagnosis had been referred for fetal echocardiography due to a suspicion of a cardiac anomaly on obstetrical ultrasound. The patients with postnatal diagnosis were referred either for cardiac tumor detection in the presence of otherwise proven tuberous sclerosis or were investigated for cardiac symptoms like a murmur due or rhythm disturbance in an otherwise healthy child.
The patients were followed up by the mean of echocardiography over 3 months to 18 years (with a mean time period of 4.8 years). The age at the cardiac rhabdomyoma detection, the number and the size of nodules at the time of detection were documented, together with their evolution on follow-up echocardiography and associated cardiac complications.
A review of the medical records all the cases with cardiac rhabdomyoma researching the major criteria for the diagnosis of tuberous sclerosis (central nervous system findings, skin findings, renal angiomyofibromas and retinal harmatomas) was carried out. The incidence of tuberous sclerosis was documented and its association to the number of tumors and their exact cardiac location statistically studied. The hypothesis was that certain locations are more likely to be related to tuberous sclerosis than others. The potential association to the number of the tumors was analyzed by using Fisher's exact test with results presented as p-value and Odd's ratio for 95% confidence intervals.

In the subgroup with precise neurological follow-up the neurodevelopmental complications were documented in terms of the presence of epilepsy, its control, the number of anti-epileptic drugs required the presence of developmental delay, requirement for special school and any associated behavioral issues. The assessment of the severity of the developmental delay (mild, moderate, severe) was based on the developmental evaluation by pediatric neurologists.

3. Results

The present study deals with 73 patients with a finding of cardiac rhabdomyoma. Among these cases, 20 patients were diagnosed in-utero at a gestational age between 20 and 35 weeks and 53 patients postnatally between 10 days and 11 years.

3.1 Number and location of cardiac rhabdomyomas

70% of the patients (51) presented with multiple cardiac rhabdomyomas while 30% of the patients (22) had a single tumor. Table 1 shows the association between the presence of multiple cardiac rhabdomyomas and the incidence of tuberous sclerosis. 4 of 73 patients had no follow up and are therefore not reported in Table 1. Tuberous sclerosis was diagnosed in 42 patients (86%) with multiple cardiac rhabdomyomas and in 13 patients (65%) with a single rhabdomyoma (p value 0.095; Odds Ratio 3.17; confidence interval at 95% of the odds ratio 0.79 to 12.92).

	Tuberous sclerosis +	Tuberous sclerosis -	Total
Multiple tumors	42	7	49
Single tumor	13	7	20
Total	55	14	69

Fisher's exact test: p value 0.095; Odd's ratio 3.17; CI at 95% Odd's ratio 0.79 to 12.92

Table 1 - Presence of multiple cardiac rhabdomyomas related to the incidence of tuberous sclerosis

The tumors were predominantly located in the left ventricle, 74% of the patients presented at least one tumor at this site. 48% of the patients had at least one tumor in the right ventricle, 44% in the interventricular septum, and a few patients had tumors in the atria (right atrium 8% and left atrium 1%), in the interatrial septum (5%) and in the pericardium (1%).

Table 2 gives the relation between these different locations and the presence of tuberous sclerosis (relative risk). The values are given in terms of numbers of patients (with and without a diagnosis of tuberous sclerosis) presenting at least one tumor in the specific locations.

	patients TS +	patients TS -	Relative risk (estimated error)
Left ventricle	44	8	5.5 (0.6)
Interventricular septum	26	6	4.3 (0.6)
Right ventricle	30	3	10.0 (2.5)
Right atrium	5	1	5.0 (2.5)
Interatrial septum	5	1	5.0 (2.5)
Left atrium	1	0	-
Pericardium	1	0	-

TS = tuberous sclerosis

Relative risk = n(TS+) / n(TS-), estimated error for n(TS-) + 1.

Table 2 - Location of the cardiac rhabdomyomas in patients with tuberous sclerosis and in patients without diagnosis of tuberous sclerosis

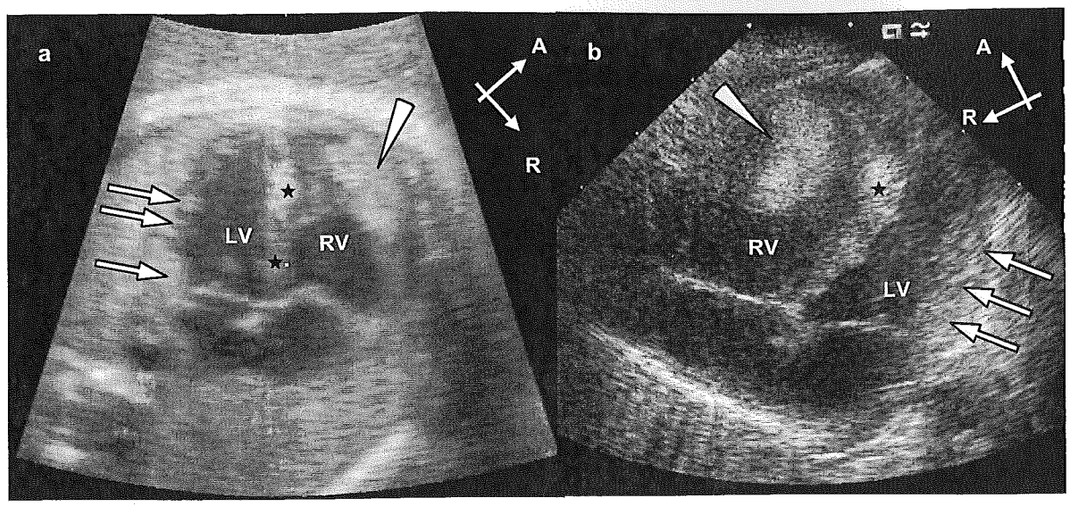
3.2 Size and evolution of cardiac rhabdomyomas

The diameter of the tumors in the prenatal group at diagnosis ranged from 1 to 37 millimeters and in the postnatal group from 2 to 55 millimeters. Figure 1 shows the fetal and postnatal echocardiography of one of the patients.

In the group diagnosed positive for tuberous sclerosis the tumors ranged from 1 to 55 millimeters in size, versus 2 to 30 millimeters for the group not affected by tuberous sclerosis.

Postnatal regression of the number and/or size of nodules was observed for 74% of patients (40) who had follow-up echocardiographic data (54). Complete resolution of cardiac rhabdomyoma was documented in 28% patients (15), and partial resolution in 46% patients (25), 19% (10) showing no changes in the tumors. In four cases nodules increased in size and new masses appeared over 6 to 14 years. Among 15 patients showing complete resolution by 6 months to 10 years of age respectively, 12 belonged to the postnatal group and 11 patients had been diagnosed for tuberous sclerosis.

A number of 6 patients showed partial resolution of big nodules along with complete resolution of smaller nodules in a time period of 1-11 years follow-up. The remaining cases demonstrated partial resolution of the rhabdomyomas or no changes of the nodules in a time period of 1–18 years follow up.



a) *b)*

Legends: A: anterior, LV: left ventricle, RV: right ventricle, R: right

Figure 1 - Fetal and postnatal cardiac rhabdomyoma: ***a)*** Fetal echocardiogram at 35 weeks of gestation and ***b)*** transthoracic echocardiogram at 2 weeks of age. Note: The two 4-chamber views show a huge rhabdomyoma in the free wall of the right ventricle (arrowhead) and smaller rhabdomyomas in the interventricular septum (stars) and in the free wall of the left ventricle (arrows).

3.3 Cardiac complications

Cardiac follow up by echocardiography was carried out for 53 patients from this population of 73 patients. These investigations showed that cardiac complications were encountered in 23% of cases and 2 of them required immediate intervention during the neonatal period. The first patient diagnosed with multiple cardiac rhabdomyoma at 34 weeks of gestational age was delivered by elective Caesarean section at 37 weeks due to significant left ventricular outflow tract obstruction by one of the nodules with a pressure gradient of almost 50 mmHg by Doppler between Aorta and LV. Successful surgical removal of the obstructing nodule was performed in the neonatal period. The second patient diagnosed with multiple cardiac rhabdomyoma at 28 weeks gestational age was delivered uneventfully but had Wolf-Parkinson-White Syndrome with refractory supraventricular tachycardia for 3 weeks after birth requiring anti-arrhythmic treatment and is currently stable under therapy. 7

other patients had rhythm disturbances, 5 in the form of occasional paroxysmal supraventricular tachycardia with or without Wolf-Parkinson-White syndrome in infancy, but were stable clinically and did not warrant any intervention, one had ventricular arrhythmia. Surgery with excision of the tumor was required in 2 patients, one with had sub-aortic obstruction and one with pulmonary outflow obstruction. One patient died at 22 days of age of cardiogenic shock due to obstruction of left ventricular filling caused by a tumor in the left ventricle (size 30x30millimeters).

No specific dimension or location of the cardiac rhabdomyoma could predict the above reported rhythm disturbances.

3.4 Neurodevelopmental complications

Tuberous sclerosis was a definite diagnosis in 76% of cases (55 patients) as they fulfilled 2 or more of the major criteria [13] for tuberous sclerosis diagnosis. Of the 55 cases with tuberous sclerosis, 20% of cases (11) did not have epilepsy whereas 80% (44) had epilepsy (Figure 2). Among those with epilepsy 32 patients had a precise neurological follow up which showed that, 6% of cases (2) are off antiepileptic drugs as they had a long seizure-free interval, 56% of cases (18) have well to moderate control (occasional seizure) on 1-2 antiepileptic drugs and 38% (12) have refractory epilepsy (several seizures per week). One patient who had pharmaco-resistent epilepsy in infancy underwent seizure surgery at 14 months of age and currently has moderately controlled epilepsy with 2 antiepileptic drugs.

Developmental delay was seen in 68% of cases (36) with tuberous sclerosis while 32% of cases (17) developed normally. Among the patients with developmental delay 25 had a follow up: 56% (14) had mild delay, 32% (8) had moderate delay and 12% (3) had severe delay. In terms of academic performance, 60% of the developmentally delayed patients (15) are in special schools, 20% (5) are in regular schools with extra support for academic work and 20% (5) are young patients not yet in school. Behavioral problems in the form of reduced attention span, aggressiveness, hyperactivity, impatience and mood fluctuations were encountered in 22% of patients (8) with developmental delay of which one patient was documented to have autism (1.8% of TS cases).

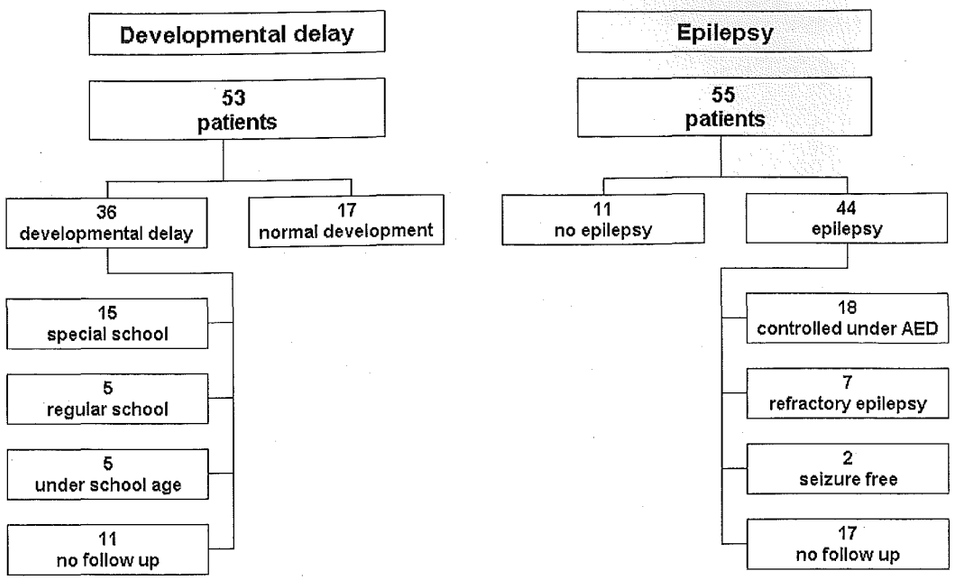


Figure 2 – Neurodevelopmental issues in patients with tuberous sclerosis
AED – antiepileptic drugs

3.5 Other findings

A major involvement of other organ systems not in relation to TS was noted in 3% of cases (2) in the series, one patient had dysmorphism with multiple organ involvement and another patient had nephroblastoma stage 4S requiring surgery with left nephrectomy in infancy.

4. Discussion

As described in the literature, the cardiac rhabdomyomas in this series of patients were benign. They showed spontaneous regression in most of the cases [14-20] and appeared between 20 and 30 weeks gestational age in any part of the heart.

The main growth of the tumors occurred between the second and the third trimester, as well as during the early postnatal period.

During prenatal life, the tumors in this population were clinically silent but intrauterine death has been reported [21, 22] mostly following fetal arrhythmia and hydrops.

Among the various cardiac complications, arrhythmias were the most often encountered problems[23-27] during the neonatal period. Supraventricular tachycardia is the commonest rhythm disturbance identified, such as in our series. Bradycardia, heart block and pre-excitation syndromes are the other arrhythmias reported.[28, 29] Arrhythmias were predominantly treatable by vagal maneuver, pharmaco-therapeutic intervention, radio-frequency ablation and/or cardioversion. Rarely the arrhythmias caused mortality.

By analyzing the size and location of the tumors in patients with arrhythmia compared to patients without rhythm disturbances, it can be concluded, that there is no specific size or location of the tumor that can predict this particular complication.

Further cardiac complications in this series included development of intra-cardiac flow obstruction, alteration of the atrio-ventricular valve function with consequent regurgitation, cardiac dysfunction and hydrops. Large left ventricular tumors can lead to severe left ventricular outflow tract obstruction in some patients, warranting surgical excision[30, 31]. Further they can very rarely cause uni-ventricular physiology in infants and pose a difficult management problem[32]. The hemodynamic complications encountered in late fetal life can be minimized by performing well timed preterm induced delivery or caesarean section. Surgery is the treatment of severe hemodynamic complications, arrhythmias or other primary cardiac tumors.[33, 34, 35]

As in this population the natural history of cardiac rhabdomyomas after birth is dominated by the neurological impairment due to tuberous sclerosis. As shown by Tworetzky et al[8], these cardiac tumors are frequently associated to tuberous sclerosis.

The importance of the diagnosis of tuberous sclerosis in a patient presenting with cardiac rhabdomyoma is exemplified in our results of neurodevelopmental complications. The results show that 80% of cases are affected by epilepsy and 63% of cases have a delayed development, data which are in accordance with the data mentioned in larger demographic series[36] for patients affected by tuberous sclerosis, reporting that 80% have epilepsy and 44-82% have neurodevelopmental difficulties.
It is important to point out that most of the patients with epilepsy have a good to moderate control of the seizure on antiepileptic drugs. Nevertheless 38% of epileptic patients have refractory epilepsy.
These results form an important issue during the prenatal counseling of parents about the further neurological and psychosocial development of their child.

On the basis of a statistical test (Fisher's exact test) and in order to enhance the predictions for the parents during the prenatal counseling, about the risks of developing tuberous sclerosis, the following statements are important to be mentioned. It must however be realized that this study although encompassing a large series on this subject, carries all the limitations of a retrospective study.
The presence of multiple cardiac tumors in patients suggests a risk factor of 6 to be affected by tuberous sclerosis. This fact has already been observed on an other population by Tworetzky *et al*[8] , but they found a substantially higher risk factor(20) than we in our series. The risk analyses for single cardiac tumors diverge even more, we found a risk factor of 1.9 to be affected by tuberous sclerosis in case of a single tumor, while Tworetzky *et al* found a factor of 0.33. This divergence could be due to a difference in the two studied populations, we excluded all other primary cardiac tumors than rhabdomyomas whereas Tworetzky *et al* included other primary tumors in the group of patients presenting with a single tumors. It is therefore extremely important to differentiate the primary tumors (rhabdomyomas, teratomas, fibromas and myxomas) during the prenatal counselling since they have a different impact on the neurological outcome related to tuberous sclerosis.
Furthermore, it can be observed that the sizes of tumors in patients affected by tuberous sclerosis are slightly bigger. In this population, tumors with a size bigger than 30millimetres were only observed in patients with tuberous sclerosis. Additional

research should be performed to conclude in a more definitive way if the size of the tumors may be a relevant factor in the diagnosis of tuberous sclerosis.

By analyzing the incidence of cardiac rhabdomyoma at different location related to the presence of tuberous sclerosis, we can conclude that there is no straightforward relationship between any of the locations and tuberous sclerosis (Table 2).

The comparison of the data between the prenatal and the postnatal group shows in effect no significant difference between the size, the cardiac complications and the development of tuberous sclerosis.

Tuberous sclerosis is an autosomal dominant Mendelian condition with a large variability of expression and a 50% familial occurrence. Chen et al [37] reported on 2 families with prenatally diagnosed cardiac rhabdomyomas and subsequently confirmed tuberous sclerosis with molecular genetic analysis. We only recently embarked on testing our patients genetically, with so far 3 positive outcomes. This should support the opinion that this condition should be suspected in all children with prenatally diagnosed cardiac rhabomyomas. Therefore, genetic testing should be applied in all patients with these cardiac tumors. Prenatal genetic analysis (of index patient and the parents to exclude polymorphism) can be considered to enable early implementation of further diagnostic evaluation and genetic counseling.[38] although the sensitivity of this technique is not yet completely elucidated. Recently, Milunsky et al [39] have performed prenatal genetic analysis of a fetus with cardiac rhabdomyomas to confirm the diagnosis of tuberous sclerosis.
However, precise prenatal molecular diagnosis of tuberous sclerosis has been not been realized yet. As long as we don't have a reliable genetic testing, the risk-calculations should be helpful for the prenatal counselling. Genetic testing should particularly be performed for prenatal diagnosis in subsequent pregnancies, if after having had an affected child both parents prove negative for TSC1 and TSC2 mutations on sequencing.

Limitations: This study included all the limitations of a retrospective study, which prevented a more concise way of reporting.

5. Conclusion

This study approaches a rare problem with potential perinatal and early infancy cardiac impact and long term neurologic sequelae, which importance is located in the numbers of cases, and not so much in the separation in to pre and post natal diagnosis.On the basis of this large population, it can be concluded that cardiac rhabdomyomas generally regress with time and surgical and/or pharmacological interventions are rarely required. Arrhythmias exist and may rarely be fatal but once adequately treated, they play a minor role in the overall outcome of the patients. The constant association of cardiac rhabdomyomas with tuberous sclerosis and the associated neurological impact however is clearly the dominating aspect in the long-term outcome and quality of life in these patients and hence calls for prenatal genetic testing and comprehensive prenatal counseling of parents whose fetuses are diagnosed with this rare disease.

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