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Clinical analysis of syringomyelia resulting from spinal hemangioblastoma in a single series of 38 consecutive patients

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ABSTRACT

objective: Syringomyelia was predominantly caused by Chiari malformation or intramedullary ependymoma. The goal of this study was to identify factors related to clinical outcomes and spinal hemangioblastoma (SH)-induced syringomyelia formation in a single series of patients.

Patient and methods: Thirty-eight patients with SH were treated with microsurgery from January 2013 to December 2018. Clinical features and related factors were retrospectively analyzed in SH patients with and without syringomyelia.

Results: Out of the total number of SH patients, 21 presented with remarkable syringomyelia, resulting in an incidence of 55.26% (21/38).Gross total resection was achieved in 36 cases (94.73%), and subtotal resection was obtained in 2 patients (5.27%). Neurological symptoms improved in 34 patients, remained stable in 2 patients and were aggravated in 2 cases during follow-up. In addition, there was a notable difference between the location of tumors and syringomyelia ($P < 0.05$). Syringomyelia occurred more frequently in the cervical segment than in any other spinal segment. Moreover, there was an association between symptom duration and clinical prognosis ($P < 0.05$). Ordinal regression analysis showed that the prognosis of middle duration groups (6–12 months) was better than early groups (0–6 months, $p < 0.05$, OR 20.21, 95%CI 2.34–336.97) and late groups (> 12 months, $p < 0.05$, OR 11.54, 95%CI 1.30–102.21). Syringomyelia collapse or reduction occurred between two weeks and 15 months after surgery. An improvement of spinal function grade after surgery was more significant in syringomyelia reduction groups ($p < 0.05$).

Conclusions: The prevalence of syringomyelia due to SH is considerably high, and the initial clinical presentation of syringomyelia resulting from SH should be emphasized. Satisfactory outcomes were achieved by effective surgery in affected patients.

1. Introduction

Intramedullary tumors are relatively rare, accounting for 2%–15% [6,8,11,16–19,22] of all tumors. Spinal hemangioblastomas (SH) rank third in prevalence behind ependymoma and astrocytoma. The most common location for hemangioblastomas involves in the posterior cranial fossae. However, spinal hemangioblastomas are relatively uncommon, accounting for only 13%–26% of all hemangioblastomas. Moreover, SH as highly vascularized, histologically benign tumors occur predominantly in a single lesion, but it can also manifest, as observed in von Hippel-Lindau (VHL) in multiple affected organs. In addition, Syringomyelia was predominantly caused by obstruction of cerebrospinal fluid flow, intramedullary tumors are part of the common reasons based on previous literatures [1,16]. However, the syringomyelia caused by SH still pay no extensive attention due to the rarity of SH currently. The SH-induced syringomyelia could cause various neurological symptoms, such as paresthesia, physical activity disorder or even joint deformities, such as Charcot joint. Unfortunately, the clinical characteristics and optimal strategies for syringomyelia caused by intramedullary SH remained unclear so far. Most importantly, The clinical profiles related to syringomyelia resulting from SH have not previously been explored in a large series of patients.

In this study, the unique clinical features and relevant factors of syringomyelia caused by SH were retrospectively analyzed in a single institutional series of 38 consecutive patients.

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Table 1
Summary of 38 patients and their tumor characteristics.

Tumor Characteristics	
Male patients, no. (%)	18 (47.4)
Median age (IQR)	46 (24)
Syringomyelia, no. (%)	21 (55.3)
Tumor position in spinal cord, no. (%)	
Intramedullary only	11 (28.9)
Intramedullary and extramedullary	27 (71.1)
Tumor location, no (%)	
Cervical	21 (47.7)
Thoracic	14 (31.8)
Lumbar	7 (15.9)
Sacral	2 (4.6)
Mean volume (mm3)	2848
VHL, no. (%)	3 (7.9)

*VHL : Von Hippel-Lindau.

2. Patient and methods

38 patients with pathologically confirmed SH cases admitted to our institution from 01-01-2013 to 01-12-2018 were retrospectively investigated in this study. The demographic features, tumor characteristics, magnetic resonance imaging (MRI) results, immunohistochemistry results, and clinical outcomes were also analyzed. All procedures were approved by the Ethics Committee for Human Experiments of the Zhengzhou University. 38 cases with SH represented approximately 20.8% (38/183) of all hemangioblastomas reported in our institution. Of these patients, 18 were male and 20 were female. Their ages ranged from 17 to 87 years old, and the median age of onset was 46 years old. Three cases had a family history, and one was diagnosed as recurrence upon admission. Four patients had multiple CNS hemangioblastomas, and 3 met the standard for VHL. The detailed demographic data on 38 cases with spinal hemangioblastomas were obtained from Tables 1 and 2

2.1. Clinical assessments

Clinical neurological assessments were evaluated using McCormick functional grades[9] before surgery, at discharge from the hospital and at the most recent follow-up. Follow-up data were acquired by telephone and in outpatient reviews. When a patient withdrew, the date and reason of discharge were noted. Each patient's age and duration of symptoms (0–6 m, 6–12 m, > 12 m), the presence of syringomyelia, the level of the syrinx, the location of the syrinx (a tumor that occupied multiple segments was considered to be in both segments), levels of inhibin-α and neuron-specific enolase (NSE), tumor volume, extent of resection was assessed in present study.

2.2. Image assessments

All patients underwent pre- and postoperative 3.0 T Magnetic Resonance Imaging. Moreover, the location of the neoplasm, the region of the affected spinal cord, the extent of syringomyelia and the tumor volume were obtained from radiological images. Tumor volume was defined as follows: the greatest anteroposterior dimension × the greatest mediolateral dimension × the greatest craniocaudal dimension × 0.5. [4]

2.3. Statistical analysis

A descriptive analysis of the baseline and univariate analyses were performed using IBM SPSS Windows 22.0. Clinical outcomes were included in the univariate analysis. The outcome variables for syringomyelia were tested using a Fisher exact test, and Spearman analysis was applied to the correlation analysis with clinical results. Ordinal logistic regression was performed to investigate risk factors including age, duration of symptoms, presence of syrinx, tumor volume and extent of resection. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical features

The most common presenting symptom of SH was pain (21 cases) followed by numbness and weakness (19 and 16 cases) and paresthesia (10 patients). Among the 38 patients, 21 had accompanying syringomyelia. Of the 20 cervical cases, 13 exhibited syringomyelia (65%). None of the lumbosacral cases were associated with syringomyelia. More details are shown in Fig. 2. Each SH occupied an average of 8.90 spinal segments, and the tumors took up 2.85 cmˆ3 of the medial intraspinal space throughout the spinal cord. The location of a neoplasm and the presence of syringomyelia (in the cervical, thoracic, and lumbosacral segments) were statistically significantly associated in our group ($p = 0.00$). However, we found no relationship between tumor volume and the length of syringomyelia.

The 38 patients underwent a total of 41 surgeries to resect 43 SH. Gross total resection was performed in 36 cases (94.74%) and subtotal resection was obtained in 2 patients (5.27%). Two patients experienced postoperative complications, including one cerebrospinal fluid leakage and one deep vein catheter thrombolysis. The patients stayed in the hospital for an average of 14.6 days. No spinal instability and deformation were observed postoperatively.

3.2. Immunohistochemistry outcomes

Cytokeratin (CK) expression was negative in all tested cases (22/22, 100%), and S-100 was found positively expressed in 28 cases (85%). There were 15 (15/29, 51.7%) cases with positive inhibin-α tests and 15 with positive NSE marker expression (15/33, 45.5%). A Ki-67 index below 5% was reported in 29 cases (29/35,82.9%). Five patients had a 10% Ki-67 level, and 1 had a 50% level. There was 1 patient who was negative from vimentin expression (1/13) and 1 who was positive for oligo-2 (Fig. 1). There was no significant relationship among NSE expression, inhibin-α expression and syringomyelia formation.

3.3. Follow-up

Thirty-three patients were followed up after an average of 30 months, and 5 cases were lost to follow-up. Neurological symptoms improved in 33 cases. However, in terms of McCormick grade, 2 cases deteriorated, 24 stayed stable, and 12 improved. During follow-up, 2 patients died of preoperative pulmonary infection and coronary disease (1 each, Table 4). There was an association between symptom duration and clinical prognosis ($P < 0.05$). Syringomyelia reduction were observed in 9 cases (9/17) with better clinical outcomes ($p = 0.006$).

4. Discussion

In recent years, despite the rapid development of stereoscopic radiotherapy, total resection in microsurgery remains the first choice for SH [3,8,12,13,18,22]. There are several striking outcomes from this study: 1) The incidence of syringomyelia caused by SH was up to 55.26% (21/38), which may be easily ignored preoperative because of its infrequency especially in sporadic cases. 2) Patients with Middle duration of 6–12 months have a better prognosis compared with an early stage of 0–6 months or late stage beyond 12 months. 3) The surgical results of hemangioblastoma were satisfactory in that most of the chief complaints improved. Improvement of spinal function grade after surgery may largely attribute to syringomyelia reduction ($P = 0.006$). 4) Once clinical symptoms and image manifestations were highly

Table 2
Demographic data on 38 cases with Spinal hemangioblastomas.

Patients. No	Age(y)/ Sex	presenting symptoms	Tumor Level	Tumor Size (mm)	syrinx(sg)	clnical grade		follow-up(mo)/ complications
						preoperative	postoperative	
1	69/F	Pain,numbness, weakness	C3-C4	10*5*5	13	II	II	2/None
2	46/F	Pain,numbness	C2-C5	40*20*10	/	I	I	14/None
3	41/M	paresthesia	T12	40*18*11	7	I	I	15/None
4	54/F	Numbness,paresthesia, bladder incontinence	L1-L2	11*11*17	/	II	I	20/None
5	23/F	Numbness,weakness	T6-T8	35*15*6	7	I	I	/
6	30/M	Weakness	L2	20*25*28	/	II	I	21/None
7	44/F	Pain, weakness	C1-T1	10*12*22	10	II	I	22/None
8	51/M	paresthesia,weakness	C4	20*10*4	/	II	I	24/None
9	15/F	Pain,weakness, hyperreflexia	T8-T10	23*17*44	7	III	II	27/None
10	22/F	Pain,numbness	C2-C5	20*15*10	/	II	I	26/None
11	45/M	Pain,numbness	T3-T4	15*15*20	14	I	I	/
12	45/M	Numbness, weakness	C2	19*19*53	2	I	I	29/None
13	39/M	Numbness,pain	L3-L4	27*13*10	/	I	I	51/None
14	63/F	Numbness,weakness, speaking dysfunction	M-C1	10*10*14	/	I	I	28/None
15	58/F	Weakness	T6-T7	20*15*10	/	III	IV	30/Paralysis
16	51/M	Pain,numbness hyperreflexia	M-C3	8*5*9	/	I	I	18/None
17	40/F	Pain,headache, weakness,dyspnea	C1-C3	30*15*5	7	II	I	/
18	36/M	Pain, paresthesia	L4	25*20*10	/	I	I	36/None
19	59/M	Palpitation, dizzy weakness,paresthesia	T3-T5	10*8*5	/	I	I	37/None
20	60/F	Pain, pareshesia	M-C1	11*12*17	/	I	I	40/None
21	60/M	Weakness,paresthesia, hyperreflexia	C7	13*10*16	/	IV	III	40/None
22	32/F	Pain	C2, cerebellum	32*18*4	/	I	I	43/None
23	71/F	Pain	L5-S1	17*20*45	/	II	II	29/Death(cornary disease)
24	57/M	Weakness, hyperreflexia dyspnea	C7-T2	60*15*15	13	IV	IV	1/Death(pulmonary infection)
25	59/F	Numbness, paresthesia	M, C2	24*23*30	2	I	I	/
26	87/M	Pain, paresthesia	L5-S1	23*34*39	/	I	II	36/first recurrence (6 mo),second recurrence (21 mo)
27	30/F	Numbness	C4	10*10*15	3	I	I	17/None
28	41/M	Pain,numbness	C2	9*13*12	13	I	I	55/None
29	51/M	Pain	C7-T1	8*10*12	5	I	I	63/None
30	54/F	Pain	M, C2-C3	30*23*22	3	II	I	10/None
31	31/M	Weakness	T1	5*5*8	14	II	I	11/None
32	48/F	Pain	T3, T11	12*13*15	14	I	I	47/None
33	35/M	Numbness, weakness	C2-C3	7*12*18	7	I	I	33/None
34	43/F	Numbness, paresthesia	C5-C6	10*20*20	8	II	I	8/None
35	65/M	Pain,numbness	T12	5*5*5	/	I	I	5/None
36	47/M	Pain,numbness	L5	15*15*7	/	I	I	7/None
37	28/F	Numbness	T3-T4	22*13*8	18	I	I	1/None
38	17/F	Pain,numbness, weakness	T2-T3	22*16*10	3	II	I	7/None

*M:Medulla oblongata Sg:segments.

suspected of SH, especially those with accompanying syringomyelia, microsurgery should be considered as the first treatment. 5) A mild correlation between the extent of resection and clinical outcomes caused by a relatively small number of cases of subtotal resection ($p = 0.075$), gross total resection of SH was recommended in present series (Table 3).

Hemangioblastoma is a relatively rare CNS neoplasm with a rich blood supply. The operation performed in our patients was supposed to

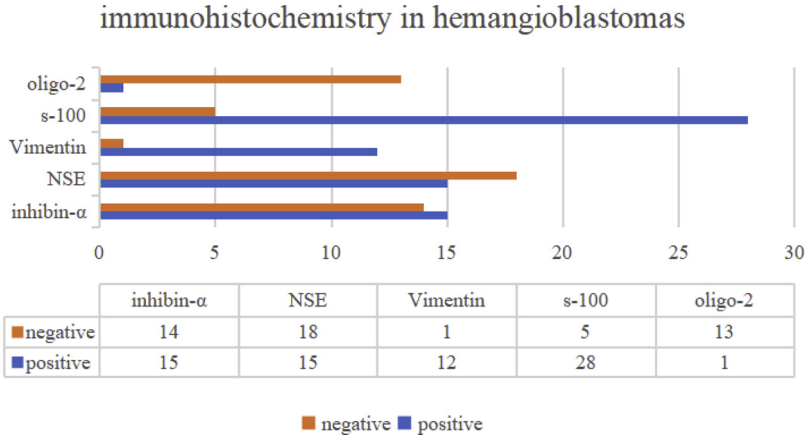

Fig. 1. Results of immunohistochemistry in hemangioblastoma in our group.

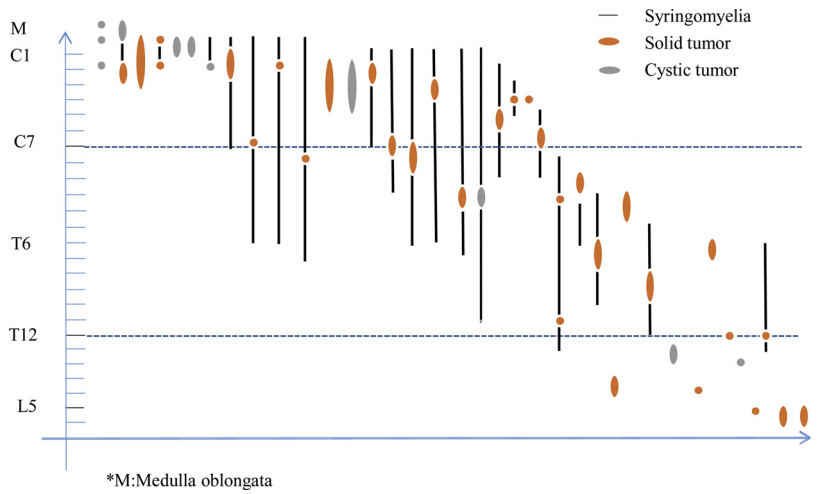

Fig. 2. 38 Cases of hemangioblastoma and syringomyelia.

Table 3
Comparison of data between the syrinx and non-syrinx groups.

Factors	Syringomyelia	Non-syringomyelia	P value
Gender			0.536
Male	9	9	
Female	12	8	
Location			0.000
Cervical	13	8	
Thoracic	11	3	
Lumbosacral	0	9	
Inhibin-α			0.723
Yes	8	8	
No	7	9	
NSE			0.407
Yes	7	8	
No	11	7	
Duration of symptoms			0.905
0-6 m	8	6	
6-12 m	6	6	
> 12 m	7	5	
Tumor volume			0.574
Age			0.064

*NSE: neuron-specific enolase.

Table 4
Potential risk factors affecting clinical prognoses.

Factors	Univariate analysis P value	Multivariate analysis OR (95%CI)	P value
Duration of symptoms	0.005		
6-12 m	—	—	—
0-6 m		21.86(2.37-201.54)	0.006
> 12 m		11.51(1.29-102.41)	0.028
Tumor volume	0.891		
Inhibin-α	0.407		
NSE	0.519		
Presence of syringomyelia	0.180		
Extent of resection	0.075		
Age	0.158		

*NSE: Neuron-specific enolase.

strictly follow the Arteriovenous Malformations excision principle. However, In contrast to a large intracranial mass, preoperative embolization and DSA examination for SH remains controversial. For a proportion of spinal hemangioblastomas which have reached the pia mater, myelotomy should be performed in the dorsal root entry zone on the affected side [20]. Eskridge and Tampieri reported sharply worsened hydrocephalus and intracranial pressure after embolization [14,15]. An uncertain indication that relied on the senior surgeon's experience led to inconclusive therapeutic effects because of potential side effects associated with diverse complications. Our experience suggests that it is essential to use neurophysiological monitoring and precise gentle operation as well as peri-tumor protection of vital structures contribute to excellent postoperative outcomes. In addition, why do patients with middle duration of 6–12 months have a better prognosis compared with an early stage of 0–6 months or late stage beyond 12 months? We speculate that one possibility for early duration groups is that tumors are too small to cause clinical symptoms. Another possible reason is that surgery for small neoplasms is more difficult, and surgical trauma makes recovery less pronounced than expected. Duration longer than 12 months requires a longer time for recovery and even prolonged compression may make spinal cord injury irreversible.

Hemangioblastoma accompanied by syringomyelia was observed in 55.26% (21/38) of the SH cases in this group. Interestingly, 16 of these cases were contained syringomyelia, while 3 and 1 cases were located in the upper and lower spinal cord, respectively, and these were not directly connected to the tumor. In a clinical setting, syringomyelia is found mainly in 1) structural defect of craniocervical junction such as Chiari malformation, 2) intramedullary neoplasms and 3) a local obstruction or mechanical distraction caused by trauma or a tethered cord. Josephson and Greitz [1] proposed a cerebrospinal fluid pressure theory that represented a new mechanism explaining the formation of syringomyelia. According to their theory, induced intramedullary pressure gradients originating from cerebrospinal fluid pulse pressure may underlie cyst formation near spinal canal obstructions. The pressure of the cerebrospinal fluid is decreased when it passes through an incomplete obstruction, and the difference between the pressure in the subarachnoid cavity and that in the intramedullary space causes intramedullary dilatation. Considering the physiological enlargement of the spinal cord and the Venturi effect [10], an upper or lower end of the syringomyelia can be detected. For lesions located in the high segment, the intramedullary pressure in the obstruction area will exert an effect. However, the Venturi effect should also be considered and may explain why a high position obstruction was more likely to be accompanied by syringomyelia. The incidence of SH was reported the third place beyond ependymomas and astrocytomas among spinal tumors, but it accompanied with the highest rate of syringomyelia [16]. Elevated vascular endothelial growth factor levels contributing to the increased vascular permeability may lead to the phenomenon [21].Due to the low morbidity of spinal hemangioblastoma, the identification of an astrocytoma cyst rather than another atypical spinal neoplasms is highly necessary. In our experience, in patients with syringomyelia of unknown cause,

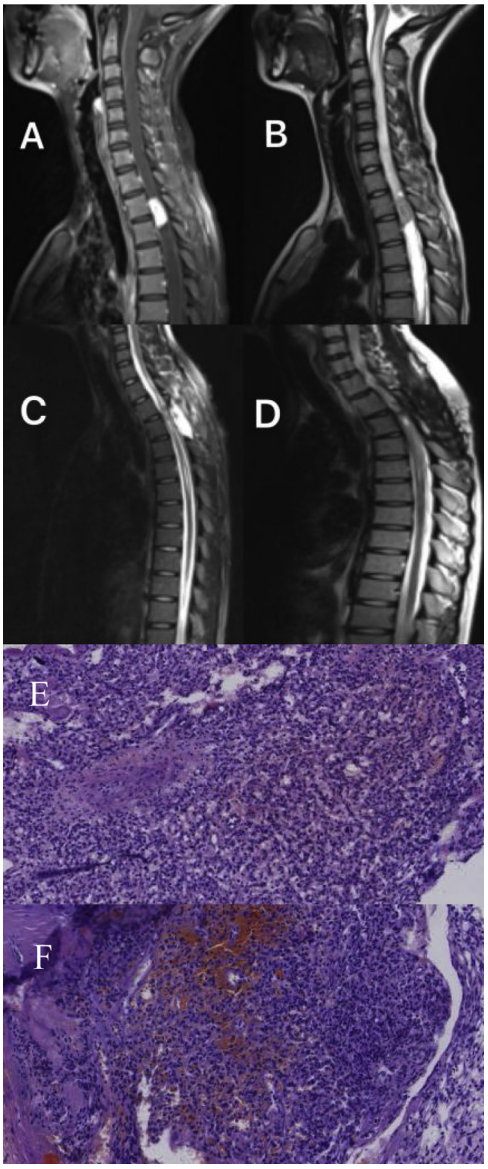

Fig. 3. A 17-year-old female presented with a chief complaint of chest numbness and pain in addition to upper limb weakness for 2 months. A physical examination revealed myodynamia of the right upper limb was grade IV and positive Hoffman's sign. Preoperative contrast-enhanced magnetic resonance images are shown. (A) Contrast-enhanced sagittal MRI showing an obvious mass at the T2-T3 level. (B) Edema from the medulla oblongata to T2 and T4-T6 syringomyelia were observed. (C) At 1 month later, a reexamination demonstrated residual T5-T6 syringomyelia. (D) The cavity medulla had nearly disappeared. (E,F)Microscopic examination: A hemangioblastoma composed of foam-like mesenchymal cells and a rich capillary network. A large number of mesenchymal cells (round and polygonal) became swollen and degenerated. Large, irregular nuclei were observed.

whole-spine contrast-enhanced MRI should be performed to exclude sporadic cyst-nodule hemangioblastoma. Equal attention should be also paid to patients with hemangioblastoma.

Histopathologically, hemangioblastoma consists mainly of a capillarity network of blood vessels and lipid-rich mesenchymal cells (Fig. 3), but debate continues over what types of cells make up the tumor tissues. In agreement with the literature, we found that vascular endothelial cells and mesenchymal cells were negative for GFAP and EMA, respectively, and that mesenchymal cells were strongly positive for NSE and S-100, suggesting that hemangioblastomas might be a neuroendocrine tumor. However, alternative findings have indicated that they are negative for neuroectodermal differentiation markers, such as syn and cga. In conclusion, the origin of the mesenchymal cells observed in these tumors remains unknown. Because there was visible heterogeneity in the distributions of the five markers in our histopathological results, we attempted to identify any potential correlation between these results and patient prognoses or syringomyelia formation. Regretfully, no positive finding between the mark of histopathology results and syringomyelia formation was observed in this study.

Patients with SH multiple lesions and recurrent tumors or VHL disease remains challenging for clinical treatment. In recent years, in addition to the continuous innovations being made in stereoscopic radiotherapy technologies, drug therapies have often been explored in case reports. Bevacizumab, thalidomide, pazopanib and other anti-angiogenic drugs have been used as prospective clinical treatments [5,7]. Albiñana et al. reported that patients with VHL syndrome who were treated with propranolol to reduce HIG-pathway dependent tumor growth showed improvements in long-term quality of life [2]. The average postoperative follow-up was only 19.9 months in this study, and longer-term follow-up studies are needed in the future.

5. Conclusion

Although SH is a relatively rare entity involved in the intramedullary tumors. However, the prevalence of syringomyelia due to SH is considerably high. Syringomyelia occurred frequently in the cervical segment and duration from 6 to 12 months showed better outcomes in present study. In addition, the initial clinical presentation of syringomyelia resulting from SH should be highlighted. Satisfactory outcomes were achieved by effective surgery in affected patients.

Statement of ethics

we certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research

Conflict of interest

The authors report no conflicts of interest in this work.

Acknowledgments

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