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ORIGINAL ARTICLE

Movement disorders identified in patients with intracranial tuberculomas

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KEYWORDS
Intracranial tuberculomas;
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Abstract
Introduction: Movement disorders have been associated with deep brain lesions. This study was performed to describe the frequency and characteristics of movement disorders in patients with intracranial tuberculomas.
Methods: Patients admitted consecutively between 1989 and 2004 to the Neurology Service of Eugenio Espejo Hospital (Quito, Ecuador), with a diagnosis of intracranial tuberculomas. All patients were examined clinically, and laboratory tests and imaging studies performed. Follow-up continued up to one year after the tuberculosis treatment was completed. A nested case-control analysis was performed to compare clinical characteristics, number and location of tuberculomas, between cases with movement disorders and controls.
Results: Forty-nine patients with tuberculomas (31.7±20.5 years; males 53.1%) were studied. We found 16 cases (32.6%; 95%CI=19.9%- 47.5%) of movement disorders: chorea (n=7; 43.8%), tremor (n=5; 31.3%), dystonia (n=3; 18.8%) and myoclonus (n=1; 6.3%). Most cases (87.6%) developed early (10.4±5.2 days of hospitalization). On admission, patients with movement disorders showed higher severity of the illness than controls (68.7 vs. 30.3%; p=.01), along with greater motor impairment (75.0 vs. 39.4%; p=.01) and sensitivity impairment (43.8 vs. 9.1%; p=.01). The cases showed higher frequency of multiple tuberculomas (68.7 vs. 36.4%), with deep brain deep (31.3 vs. 21.2%) and more severe motor impairment (25.0 vs. 12.1%).
Conclusions: Our results suggest a causal relationship between tuberculomas and movement disorders. Deep location and multiple tuberculomas may increase the risk of develop movement disorders.

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PALABRAS CLAVE
Tuberculomas intracraneales;
Trastornos del movimiento;
Patogénesis;
Enfermedades del sistema nervioso central

Movimientos anormales identificados en pacientes con tuberculomas intracraneales

Resumen
Introducción: Los movimientos involuntarios anormales (MIA) se han asociado con lesiones en estructuras profundas del cerebro. El objetivo del estudio fue describir la frecuencia y características de MIA en pacientes con tuberculomas intracraneales.
Métodos: Se incluyeron los pacientes ingresados consecutivamente en el Servicio de Neurología del Hospital Eugenio Espejo (Quito-Ecuador) entre 1989 y 2004 con diagnóstico de tuberculomas intracraneales. Todos los pacientes fueron examinados clínicamente, se realizaron exámenes de laboratorio y estudios de imagen. El período de seguimiento se prolongó hasta un año después del tratamiento antituberculoso. Dentro de la cohorte se diferenció dos grupos: casos incidentes con MIA y controles. Se compararon las características clínicas, número y localización de los tuberculomas.
Resultados: Se estudiaron 49 pacientes (edad media 31,7 ± 20,5 años; sexo masculino 53,1%). Hubo 16 casos incidentes (32,6%; IC 95%= 19,9%- 47,5%) de MIA: corea (n = 7; 43,8%), temblor (n = 5; 31,3%), distonía (n = 3; 18,8%) y mioclonías (n = 1; 6,3%). La mayoría de casos (87,6%) se desarrollaron tempranamente (10,4 ± 5,2 días de hospitalización). Al ingreso los pacientes con MIA mostraron mayor severidad de la enfermedad que los controles (68,7 vs. 30,3%; p = 0,01), tuvieron mayor déficit motor (75,% vs. 39,4%; p = 0,01) y sensitivo (43,8 vs. 9.1%; p = 0,01). En los casos fueron más frecuentes los tuberculomas múltiples (68,7 vs. 364%), la localización supratentorial profunda (31,3 vs. 21,2%) y las secuelas motoras (25,0 vs. 12.1%).
Conclusiones: Los resultados sugieren una relación causal entre tuberculomas y MIA. La localización profunda y la presencia de tuberculomas múltiples incrementarían el riesgo para desarrollar MIA.

Introduction

Movement disorders (MDs) have been associated with focal unilateral or bilateral lesions deep in the brain. Other brain areas have also been involved in their incidence.[1-3]

In tuberculous meningitis, 18% of patients can present MD.[4] Movement disorders in these patients have been related with the presence of ischemic lesions, hydrocephalus, oedema and bacterial neurotoxins.[4]

Isolated cases of MD have been described in patients with intracranial tuberculomas.[2,5-10] In developing countries, these lesions represent 15% to 20% of expansive intracranial processes.[11-13] Intracranial tuberculomas can be single or multiple, be located in different areas and present with neurological symptoms and variable clinical courses. Neuroimaging studies play a very important role in their diagnosis.[14]

The appearance of MD in patients with intracranial tuberculomas could be due to various pathogenic mechanisms. The frequency and association of risk between both conditions have not been estimated. Achieving better understanding of the causal reason requires specific research on the topic.[15] In this article, we present the results of a study undertaken to identify the development of MD in patients who were carriers of intracranial tuberculomas and we describe some data that supports the causal relationship between both disorders.

Patients and methods

The research project was approved by the Bioethics Committee of the Central University of Ecuador, and was carried out in the Neurology Clinic Department at the Hospital Eugenio Espejo in the city of Quito. To form the study cohort, all patients admitted consecutively during 1989-2004 who were included in the "Central Nervous System Tuberculosis Register" and were diagnosed with intracranial tuberculomas were considered. The diagnosis was established by computerised tomography and/or magnetic resonance, and by one or more of the following findings: cerebrospinal fluid (CSF) culture or Ziehl stain positive for *Mycobacterium tuberculosis*, CSF that suggested meningeal inflammation and a positive ELISA test; pathological or autopsy findings compatible with tuberculosis or tuberculosis in other tissues or body fluids.

Additionally, patients needed to show a positive Mantoux test, a thorax x-ray compatible with pulmonary tuberculosis, basal uptake in the computerised tomography or magnetic resonance, positive ADA in the CSF, previous history of tuberculosis and a favourable clinical response to tuberculosis treatment. Other concurrent brain pathologies such as cerebral vascular disease, intracranial neoplasms, neurocysticercosis and cerebral toxoplasmosis, as well as movement disorders, neuroleptic use and prior hydrocephalus were considered as exclusion criteria.

All patients received daily TB treatment that consisted of 2 stages: an initial hospitalised stage that lasted 2 months and then an out-patient one that lasted 4, 7, 10 or more months as necessary. During hospitalisation, the patients were assessed daily and received isoniazid, rifampin and pyrazinamide at standard doses. In some cases, we had to add ethambutol or streptomycin. Assessment was weekly during the out-patient phase and the treatment consisted of isoniazid and rifampicin. Patients who had impairment of consciousness or intracranial hypertension and focal deficit received a steroid treatment with prednisone. Treatment was considered to have concluded when the patient was asymptomatic, with normal imaging studies and CSF within normal limits.

The patient follow-up period was started on the first day of hospitalisation and continued until a year after the treatment had finished or, if applicable, when the patient died. The following MD incident cases were identified within the cohort: chorea-ballism, dystonia, tremor and myoclonus, defined in accordance with previously established criteria.[4,16-19] The day the movement disorder started was recorded in each case and a new neuroimaging study was carried out to eliminate other possible aetiological causes.

By considering the initial neuroimaging findings, we classified the location of the tuberculomas into supratentorial (superficial or deep), infratentorial and subarachnoid. We determined the number of tuberculomas and condensed the findings into two possible categories: single or multiple tuberculomas. We also recorded the presence of meningeal enhancement, ischemic injury and hydrocephalus.

Within the total group, the variables recorded were demographic data, personal history, duration of neurological symptoms, presence of seizures before admittance and the main characteristics of the symptoms on hospital admittance, including level of consciousness, presence of papilloedema, motor deficit, sensory deficit and CSF characteristics.

The seriousness of the disease on admittance was assessed with a modified scale of the British Medical Research Council[1-3] into 3 categories:

1. Stage I: patient with an absence of definitive neurological symptoms on admittance or during pre-admittance history, with or without intracranial hypertension.
2. Stage II: patient with slight to moderate impairment of consciousness and/or focal neurological signs such as cranial nerve palsies or hemiparesis, with or without hypertension.
3. Stage III: patient with severe impairment of consciousness, seizures, with or without intracranial hypertension and focal neurological signs such as hemiplegia and paraplegia.

The functional prognosis of the patients was established using the modified Smith[20,21] scale in 4 categories: a) patient totally recovered, with no neurological deficit; b) patient with slight sequelae who did not need assistance in any activity; c) patient with moderate sequelae who required help for certain activities; and d) patient with serious sequelae who depended on others to carry out activities in daily life. The MD evolution was qualified as complete, partial or no improvement.

The information analysis was carried out mainly with descriptive and inferential statistics, summarising the data as means (± standard deviation) or percentages. To estimate MD frequency precision, we calculated a confidence interval of 95% of the proportion. For exploratory purposes of the causal relationship between tuberculomas and MD, we formed 2 groups nested within the cohort: the first with patients who developed MD (cases) and the other with the rest of the subjects who did not present movement disorders until the end of the follow-up (controls). The characteristics of their clinical symptoms, the severity on admittance, prognosis on discharge and neuroimaging findings (mainly the location and number of tuberculomas) were compared between both groups. In these analyses, we used Student's t-test and x^2 test with Yates correction to compare the means and proportions as appropriate according to the type of variable, considering a value of $P<.05$ as a statistically-significant difference.

Results

A total of 49 patients with intracranial tuberculomas were studied (mean age 31.7±20.5 years old; male gender 53.1%). During the follow-up period, we identified 16 cases (32.6%; CI 95%=19.9%-47.5%) with MD: chorea (n=7; 43.8%), tremor (n=5; 31.3%), dystonia (n=3; 18.8%) and myoclonus (n=1; 6.3%). The majority of these patients were females (n=10). Four patients were under the age of 10 and 37.6% between 21 and 40 years of age. The largest percentage of MD cases appeared during hospitalisation (n=14; 87.6%) during a mean time period of 10.4±5.2 days. Two patients (12.5%) developed movement disorders during the out-patient treatment phase (table 1).

The severity of the disease on hospital admittance was greater (Stage II or III in the modified BMRC scale) in cases than in controls (68.7% vs 30.3%; $P=.01$), and motor deficit (75.0% vs 39.4%; $P=.01$) and sensory deficit (43.8% vs. 9.1%; $P=.01$) were more frequent. The remaining clinical characteristics were similar in both groups (table 2).

The most common location of the tuberculomas was supratentorial (n=39; 79.6%), with a predominance at a superficial level. Infratentorial and subarachnoids were rare (22.4 and 12.2% respectively) (table 3). The total number of tuberculomas identified by neuroimaging had a range of between 1 and 24. The presence of multiple tuberculomas was significantly more common in MD cases that in the control group (68.8% vs 36.4%; $P=.03$).

Basal ganglia compromise was more frequent in the cases than in the controls (31.3% vs 21.2%). In the latter, we mainly saw superficial supratentorial tuberculomas (43.8% vs 60.6%). However, these differences were not statistically significant. There were no differences in the infratentorial locations 25.0% vs 21.2%) and subarachnoid locations (12.5% vs 12.1%).

In the cases with basal ganglia compromise (Case 2, fig. 1), 1 patient presented generalised chorea with focal deficit. Four had hemichorea and 2, focal chorea - all of them with ipsilateral deficit. A patient with bilateral tremor in the upper limbs did not have motor deficit and another had motor deficit contralateral to abnormal movement. A

Table 1 Clinical characteristics and prognosis of 16 cases with intracranial tuberculomas and movement disorders

	Chorea (n=7)	Dystonia (n=3)	Tremor (n=5)	Myoclonus (n=1)
Male sex	1	1	3	1
Age (years)	20.2±11.8	26.6±19.7	53.2±25.5	2.0±0.0
Pre-admission symptoms				
Between 3 and 4 weeks	1	2	—	1
More than 4 weeks	6	1	5	—
Disease severity BMRCm				
Stage I	1	—	4	—
Stage II	5	3	1	1
Stage III	1	—	—	—
Location of the tuberculomas				
Superficial supratentorial	2	—	4	1
Deep supratentorial	5	—	—	—
Infratentorial	2	1	1	—
Subarachnoid	—	1	—	1
Multiple tuberculomas	5	1	4	1
Appearance of MD				
Hospital	7	3	3	1
Out-patient	—	—	2	—
Time of onset (days)	7.4±4.5	16.6±2.8	11.0±4.9	10.0±0.0
MD condition on discharge				
Complete improvement	6	3	3	1
Partial improvement	1	—	1	—
With no change	—	—	1	—

The data are presented as number of patients or mean±SD.
BMRCm: Modified British Medical Research Council scale; MD: movement disorders. For more details on categories, see section "Subjects and methods".

patient showed dystonia with tetraparesis and another had motor deficit contralateral to the dystonia (table 4).

The plans for TB treatment were similar in both groups of patients. The most commonly used (59.2%) during the first phase was a combined therapy of isoniazid, rifampicin and pyrazinamide. The duration of the treatment in months was 6 (12.2%), 9 (18.3%), 12 (24.5%) or more than 12 months. In 13 cases that presented MD (81.3%), the TB treatment was prolonged more than 12 months and corticoid use was more frequent (50.0% vs 21.2%). There were 6 patients (12.2%) who had a paradoxical response during treatment, 2 of them with MD (12.5%). Two patients (1 from each group) were submitted to neurosurgery because of hydrocephalus.

When the treatment was finished, 73.5% of patients showed a complete recovery in tuberculomas (table 2). There were cognitive sequelae in 3 patients in the control group. The presence of motor sequelae was more common in cases with MD (25.0% vs 12.1%).

The evolution of MD was favourable in 13 patients, whose movement disorder disappeared once the treatment was finished. A patient with tremor and another with chorea showed partial improvement during treatment. The patient with chorea died and the patient with tremor improved once the treatment was finished. A patient with tremor did not have significant improvement of the movement disorder (table 1). There were a total of 6 deaths (12.2%) during the follow-up period, 2 of which belonged to the group of cases.

Discussion

Large series of patients with intracranial tuberculomas have been published.[22,23] However, the majority of MD cases of this type of pathology correspond to isolated reports.[1,5-10] Due to the fact that patients with tuberculomas have been studied at neurosurgical centres preferentially, there has been difficulty and little interest in recognising them. The lack of identification and recording of MD when it is not the main variable of the study, as well as the lack of a systematic use of neuroimaging studies and the rapid improvement some patients can present after having started TB treatment,

Table 2 Clinical findings (from cerebrospinal fluid), neuroimaging and prognosis of 49 patients with intracranial tuberculomas

	MD Cases N=16 (%)	Controls N=33 (%)	Total N=49 (%)
Male sex	6 (37.5)	20 (60.6)	26 (53.1)
Age (mean±SD)	30.6±23.6	32.2±19.2	31.7±20.5
Duration of symptoms pre-admittance			
Less than 1 week	—	5 (15.2)	5 (10.2)
Between 1 and 2 weeks	1 (6.3)	5 (15.2)	6 (12.2)
Between 3 and 4 weeks	3 (18.8)	5 (15.2)	8 (16.3)
More than 4 weeks	12 (75.0)	18 (54.4)	30 (61.2)
Seizures in the previous 24 hours	1 (6.3)	9 (27.3)	10 (20.4)
Episodes of confusion in the previous 24 hours	6 (37.5)	21 (63.6)	27 (55.1)
Papilloedema	8 (50.0)	9 (25.3)	17 (34.7)
Disease severity BMRCm			
Stage I*	5 (31.3)	23 (69.7)	28 (57.1)
Stage II*	10 (62.5)	8 (24.2)	18 (36.7)
Stage III	1 (6.2)	2 (6.1)	3 (6.1)
Level of consciousness			
Normal	9 (56.3)	19 (57.6)	28 (57.1)
Confusion	6 (37.5)	11 (33.3)	17 (34.7)
Stupor	1 (6.3)	1 (3.0)	2 (4.1)
Coma	—	2 (6.1)	2 (4.1)
*Motor deficit on admittance**	12 (75.0)	13 (39.4)	25 (51.0)
*Sensory deficit on admittance**	7 (43.8)	3 (9.1)	10 (20.4)
Findings in the cerebrospinal fluid			
Pleocytosis	11 (68.8)	23 (69.7)	34 (69.4)
Increase in proteins	8 (50.0)	23 (69.7)	31 (63.3)
Neuroimaging findings			
Meningeal enhancement	4 (25.0)	9 (27.3)	13 (26.5)
Ischemic lesion	3 (18.8)	12 (36.4)	15 (30.6)
Hydrocephalus	10 (62.5)	17 (51.5)	27 (55.1)
Functional prognosis on discharge			
Totally recovered	11 (68.8)	25 (75.8)	36 (73.5)
Mild sequelae	3 (18.8)	2 (6.1)	5 (10.2)
Moderate sequelae	—	1 (3.0)	1 (2.0)
Serious sequelae	2 (12.5)	5 (15.2)	7 (14.3)
Cognitive deficit on discharge	—	3 (9.1)	3 (6.1)
Motor deficit on discharge	4 (25.0)	4 (12.1)	8 (16.3)
Deaths during the follow-up	2 (12.5)	4 (12.1)	6 (12.2)

The data are presented as the number (%).
BMRCm: Modified British Medical Research Council scale; MD: movement disorders. For more details on the categories, see section "Subjects and methods".
* $P=.01$ in the comparison between case and control groups.

are factors that may have contributed to the low recognition of these movement disorders.[15]

From the information available, our study is the first that has been carried out on a cohort of patients with brain tuberculomas, and with the prime aim of investigating the presence of movement disorders. The frequency of movement disorders identified (32.6%) is higher than that previously found in patients with tuberculous meningitis (18%; CI 95% 0.5 and 18.6%).[4] The findings allow us to estimate that between 20%and 47%of patients with these lesions can present some type of MD, with a generally early appearance and favourable clinical evolution.

Previous studies have reported that intracranial tuberculomas tend to be located in the corticomedullary and paraventricular junction, and less frequently in the basal ganglia, brain stem or cerebellum.[11,13,14,24] The patients

Table 3 Location of brain tuberculomas in 49 patients with and without movement disorders

	MD Cases N=16 (%)	Controls N=33 (%)	Total N=49 (%)
Multiple tuberculomas*	11 (68.8)	12 (36.4)	23 (46.9)
Location of the tuberculomas			
Supratentorial	12 (75.0)	27 (81.8)	39 (79.6)
Superficial	7 (43.8)	20 (60.6)	27 (55.1)
Deep	5 (31.3)	7 (21.2)	12 (24.5)
Infratentorial	4 (25.0)	7 (21.2)	11 (22.4)
Subarachnoid	2 (12.5)	4 (12.1)	6 (12.2)

The data are presented as the number (%). The patients could have tuberculomas with more than one simultaneous location. MD: movement disorders.

* $P=.03$ in the comparison between case and control groups.

studied who developed some type of MD presented multiple tuberculomas, generally compromising the deep brain areas, a location that can influence the appearance of MD.

In patients with chorea, we found a very frequent relationship between motor deficit and abnormal movement (87.5%). This suggests that when patients have this

Figure 1 A. Tomography without contrast that shows left thalamic isodense lesion accompanied by a significant perifocal vasogenic oedema, mass effect and lateral ventricle dilation. B. Tomography with contrast that shows a somewhat irregular reinforcement ring at a left thalamic level, with an isodense core with brain parenchyma.

Table 4 Clinical characteristics of imaging and prognosis in 16 patients with intracranial tuberculomas and movement disorders

No.	Age	Gender	BMRC	Onset MD	MD type	Motor deficit	CT or MRI	Prognosis
1	9	F	1		Left hemichorea	Left Hemiparesis	Frontal and right thalamic granuloma, hydrocephalus	1
2	16	F	2		Generalised chorea	Right Hemiparesis	Hydrocephalus, left thalamic granuloma	1
3	28	F	2		Right hemichorea	Right Hemiparesis	Hydrocephalus, frontoparietal and left thalamic granuloma	1
4	22	M	2		Right hemichorea	Right Hemiparesis	Hydrocephalus, caudal and left thalamic granuloma	2
5	8	F	2		Right hemichorea	Right Hemiparesis	Parietal and left thalamic granuloma and right cerebellum	1
6	17	F	2		URL Chorea	-	Granuloma and left frontotemporal abscess	2
7	42	F	1		URL Chorea	-	Granuloma right cerebellar hemisphere	Died
8	27	F	2		Right hemichorea	Right Hemiparesis	Granulomas in thalamus and left frontotemporal	2
9	31	F	1		URL Tremor	Right Hemiparesis	Superficial supratentorial granulomas in figure of eight	1
10	25	F	2		ULL Tremor	Left Hemiparesis	Right parietal granuloma	1
11	79	M	2		ULs Tremor	-	Right parietal and left frontal granuloma	1
12	40	F	1		URL Tremor	Left Hemiparesis	Right sylvian fissure granuloma, hydrocephalus	1
13	79	M	1		URL Tremor	-	Frontoparietal and left thalamic granuloma	0
14	36	M	2		Dystonia and LLs tremor	Tetraparesis	Hydrocephalus, bilateral thalamic infarcts, bilateral sylvian fissure granulomas	1
15	42	F	2		Dystonia LLs	Right Hemiparesis	Vermis granuloma and in left cerebellar hemisphere, hydrocephalus	1
16	20	F	2		Upper & lower limbs, cortical myoclonus	-	Right frontal abscess and right frontotemporal subdural abscess	2

-: absent; BMRC: British Medical Research Council; MRI: magnetic resonance imaging; MD: movement disorders; URL: upper right limb; ULL: upper left limb; LLs: lower limbs; ULs: upper limbs; CT: computerised tomography.

relationship and show 1 or several expansive lesions in imaging, especially in the basal ganglia, it is highly likely that their aetiology is tubercular.

The pathogenesis of the movement disorders caused by intracranial tuberculomas could be related to a pressure-distortion mechanism. If the tuberculoma simultaneously has oedema or ischemia, the distortion effects on the basal ganglia will be greater.[1,5] Additionally, toxic bacterial factors and hydrocephalus secondary to the presence of tuberculomas could contribute to the appearance of abnormal movements.[2] As the cerebellum and brain stem are structures related to the basal ganglia, an infratentorial location of the tuberculomas could also be related to the presence of movement disorders.[1,7,9]

The probability that a patient with brain tuberculomas could develop MD would be fundamentally related to the location of the lesion and its effects,[1,2,5] compromising excitatory or inhibitory basal ganglia pathways or with their connections with the thalamus, subthalamus, brain stem, cerebellum and cerebral cortex. A deep location and the presence of multiple tuberculomas increase the risk of patients developing MD.[1,4] The high incidence rate of MD in patients with tuberculomas suggests that there are non-identified factors that could increase the risk of developing abnormal movements.

The treatment of choice for tuberculomas is pharmacological. There is an 85% rate of patients who respond well to TB therapy.[11,13,25] This finding is confirmed by the total recovery in the majority of patients investigated, including MD resolution in practically all cases. However, when the patient presents progressive intracranial hypertension or there is a lack of response to pharmacological treatment (as in 2 of our patients), surgical decompression is indicated.[13,25,26]

Just as in this article, cases of paradoxical response with brain tuberculoma development or increase in their size have been described during treatment.[12,26,27] The reason for this behaviour is not well explained, but is probably related to an immune response mediated by lymphocytes and macrophages.[6,27]

The presence of movement disorders associated to brain tuberculomas can complicate the diagnosis and handling of the patient. An abnormal movement with is initially acute can be the first clinical manifestation of a tuberculoma. In a patient with MD who shows widespread lesions in neuroimaging studies, especially if they are located deep and are multiple, there is a strong possibility of diagnosing intracranial tuberculoma.

The results of this study strongly suggest a causal relationship between tuberculomas and MD; however, it is necessary to confirm these findings with new research. Although the influence of selection and measurement bias could be reduced because the groups that were compared came from the same cohort and a uniform procedure was followed for the assessment of the patients, the fact that all the patients were carriers of tuberculomas made it impossible to determine the real association with this exposure to risk. In addition, the precision of the results is conditioned by the number of subjects, which also limited having sufficient statistical power to carry out causal association tests.

Due to the fact that the appearance of MD can be an uncommon event in patients with CNS tuberculosis, the causal association should be assessed through a specific design of cases and causes.[28-30] A study with these characteristics was recently designed by our team and we hope that its findings allow us to better understand the risk of MD in patients with tuberculomas.[15]

Conflict of interest

The authors have no conflict of interest to declare.

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